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RIMINI
Hotel Savoia

13-14 aprile 2026

GdL istiocitosi

Elena Sieni

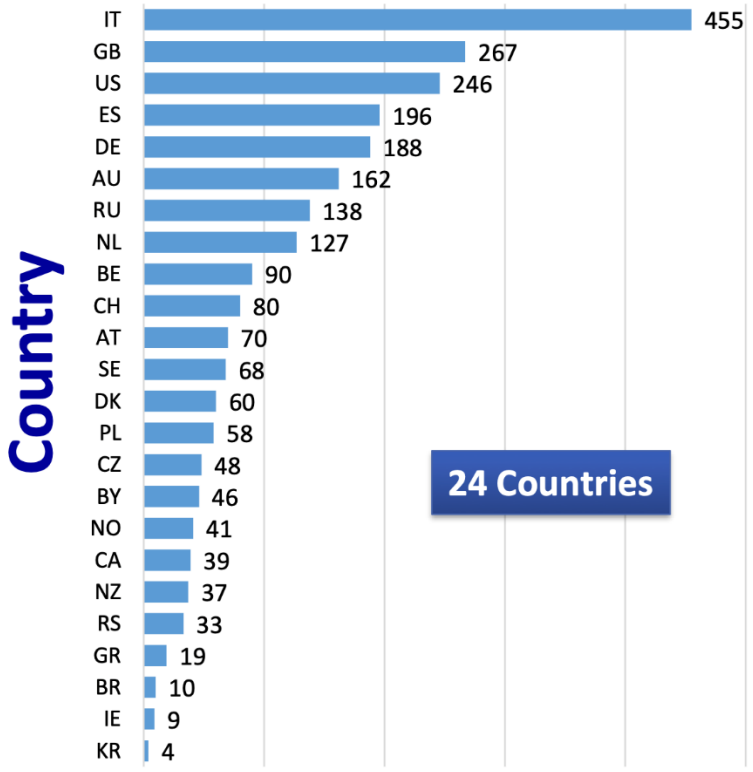
Oncoematololgia Meyer, Firenze

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

LCH-IV accrual, N=2491 (Sept 2025)

Recruitment stop: Nov 30, 2025 → The study is open for follow-up



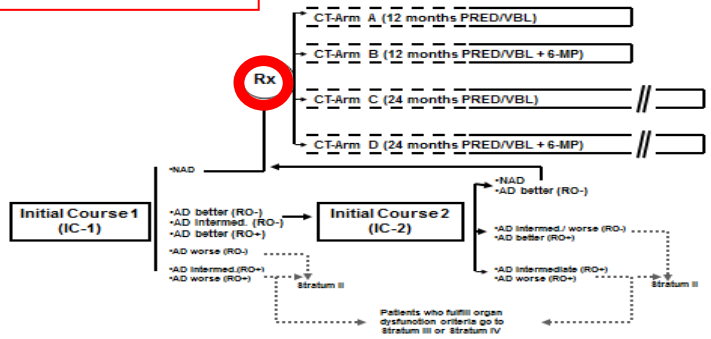
Italian centers	PI	n=510
ANCONA	Simona Gobbi	8
BARI	Nicola Santoro	7
BOLOGNA AOSP	Fraia Melchionda	8
BRESCIA	Fulvio Porta	10
CAGLIARI	Rosamaria Mura	16
GENOVA	Massimo Conte	19
MEYER	Elena Sieni	75
MILANO IRCCS TUMORI	Stefano Chiaravalli	68
MODENA	Monica Cellini	3
MONZA	Paola Corti	24
NAPOLI SANTOBONO	Carmen De Fusco	44
NAPOLI VANVITELLI	Francesca Rossi	0
PADOVA	Alessandra Todesco	34
PALERMO	Antonino Trizzino	12
PARMA	Angelica Barone	5
PAVIA	Marco Zecca	0
PERUGIA	Maurizio Caniglia	4
PESCARA	Nicole Santoro	1
PISA	Mariacristina Menconi	1
RIMINI	Roberta Pericoli	8
ROMA OPBG	Franco Locatelli	122
ROMA LA SAPIENZA	Giona Fiorina	2
SAN GIOVANNI ROTONDO	Anita Spirito	5
TARANTO	Letizia Brescia	0
TORINO	Franca Fagioli	31
TRIESTE	Marco Rabusin	0
VERONA	Simone Cesaro	4

21/24 centres

LCH-IV STRATUM I - GROUP 1

MS-LCH

383/446 (86%)



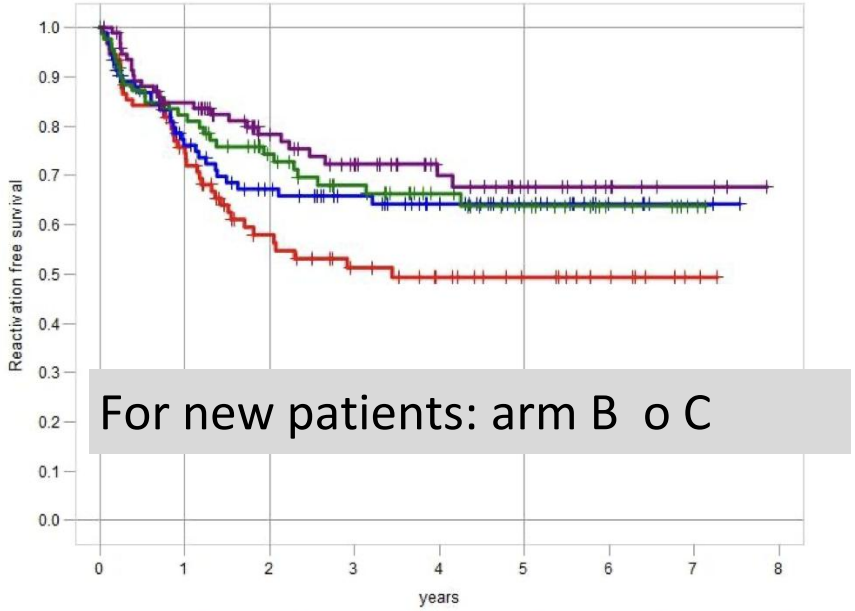
N=612

RO+ 182

M 347, F 265

Median age 1.9 y

Randomisation stop August 25, 2025



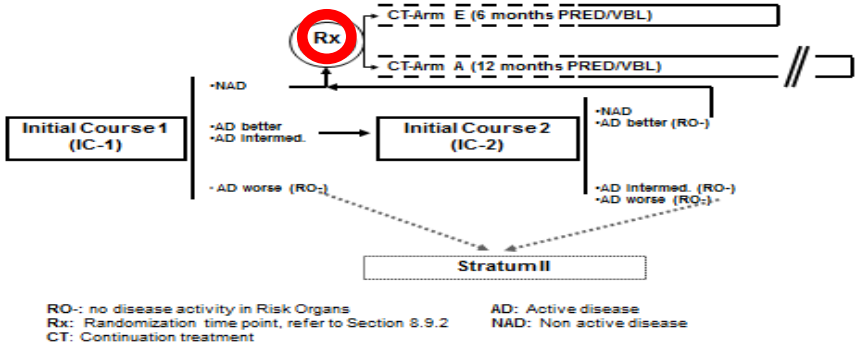
For new patients: arm B o C

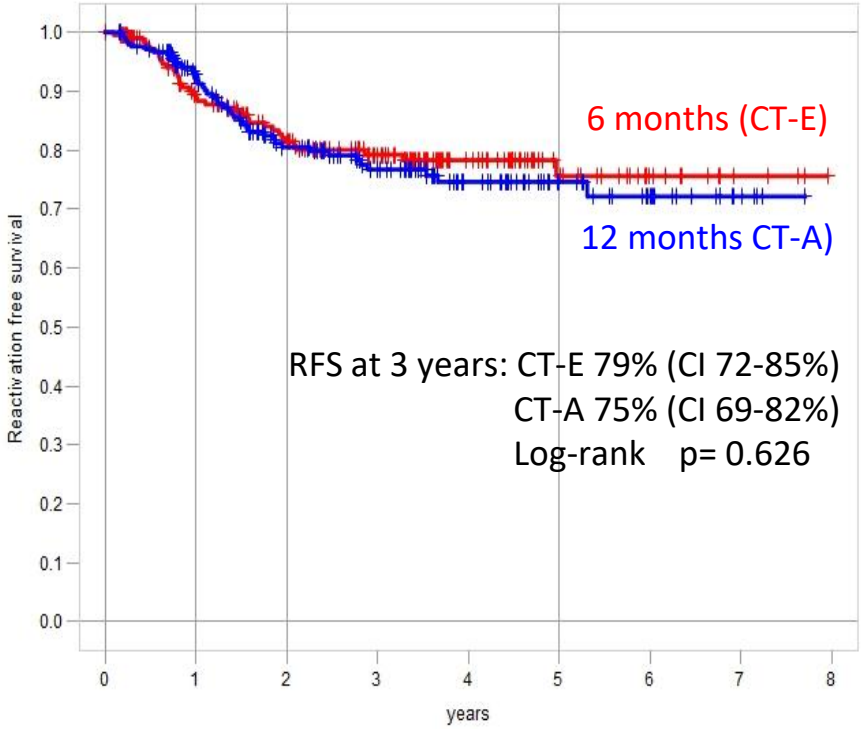
	Patients	Events	1-yrs. RFS	2-yrs. RFS	5-yrs. RFS	p-value
A: 12 months PRED/VPL	92	39	0.76±0.05	0.58±0.06	0.49±0.06	0.060
B: 12 months PRED/VPL+6-MP	94	30	0.76±0.05	0.67±0.05	0.64±0.05	.
C: 24 months PRED/VPL	89	27	0.82±0.04	0.74±0.05	0.64±0.06	.
D: 24 months PRED/VPL+6-MP	95	25	0.85±0.04	0.78±0.04	0.68±0.06	.

LCH-IV STRATUM I - GROUP 2

SS-LCH patients with isolated “CNS-Risk” or MFB lesions

441/495 (89%) randomized





N=763

428 MFB; 428 CNS-risk; 166 MFB+CNS-risk

M 443, F 320

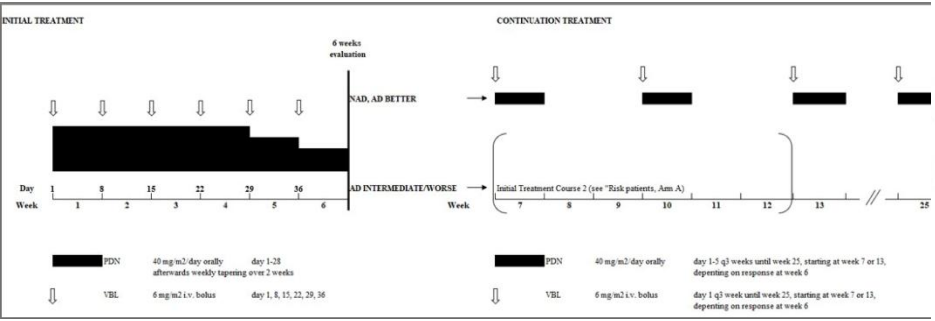
Median age: 5.3 y

Randomisation stop May 31, 2022

Treatment of MFB and SS skeletal LCH: LCH-III Study Results

2001–2008

n=381/455 evaluable, median FUP: 3.76 y



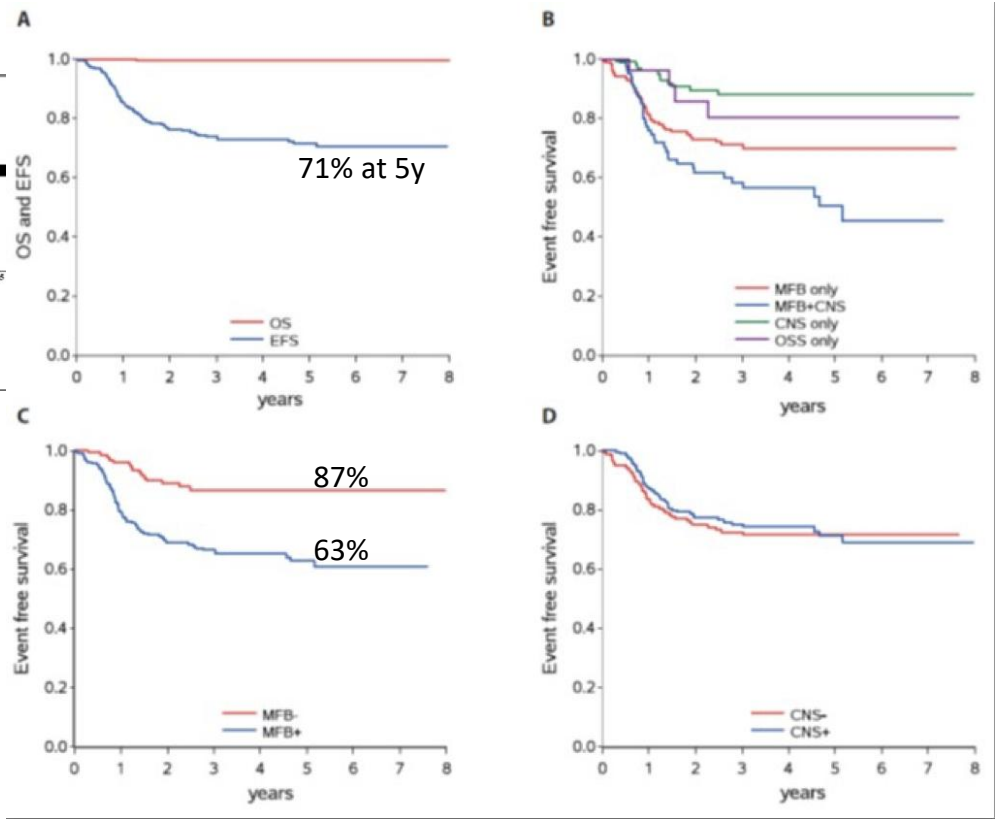
Response at week 6: 83%

Overall survival: 100% at 5 years.

EFS: 71% at 5 years

MFB: > relapse risk

NAD at week 6: < relapse risk



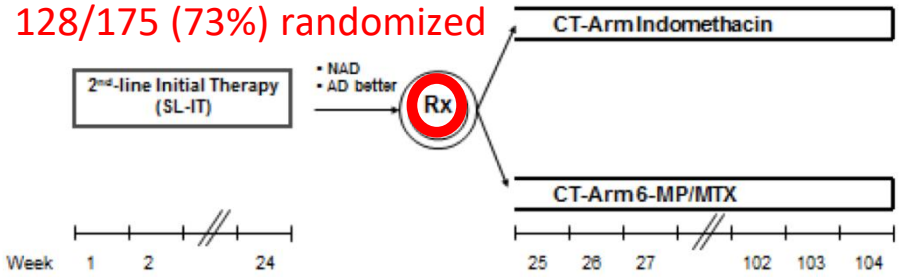
Astigarraga I…Milen Minkov et al. Submitted

Stratum II

II line (except RO+ very high risk)

Therapy-plan

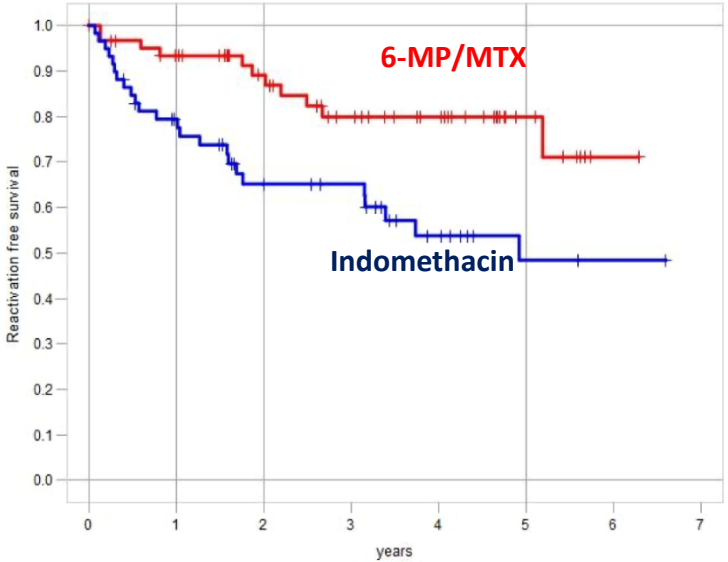
128/175 (73%) randomized



N=231

Median age at diagnosis: 2.2 y

Median age at study enrollment: 3.0 y



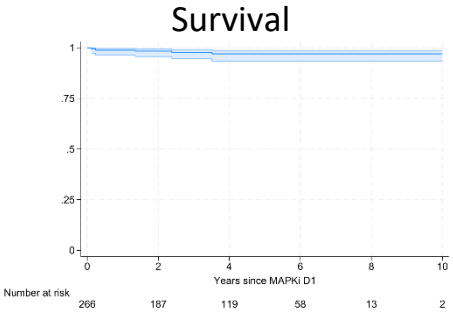
	Patients	Events	1-yrs RFS	2-yrs. RFS	5-yrs. RFS	p-value
6-MP/MTX	62	11	0.93±0.03	0.89±0.04	0.80±0.06	0.004
Indomethacin	59	25	0.79±0.05	0.65±0.07	0.48±0.08	.

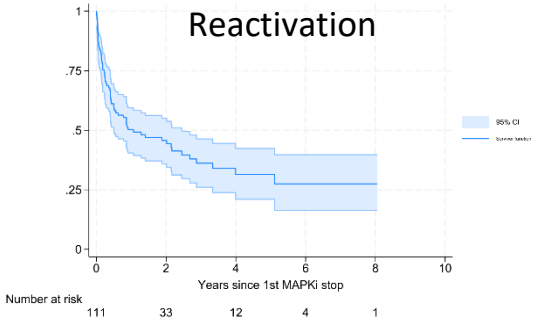
blood advances February 2026

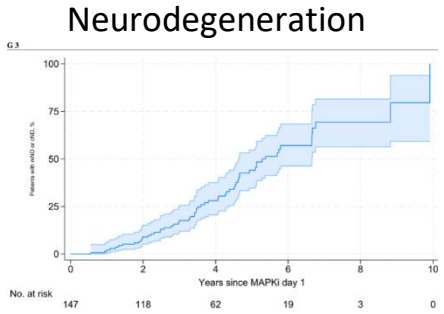
Long-term inhibition of childhood refractory-LCH: an observational study on 288 pts

Jean Donadieu et al. ECHO network. AIEOP: Florence, Rome OPBG, Naple Paus, Milan INT, Monza, Padua

Short term response
in RO+r and RO-r
Long term response
in Lung and ND





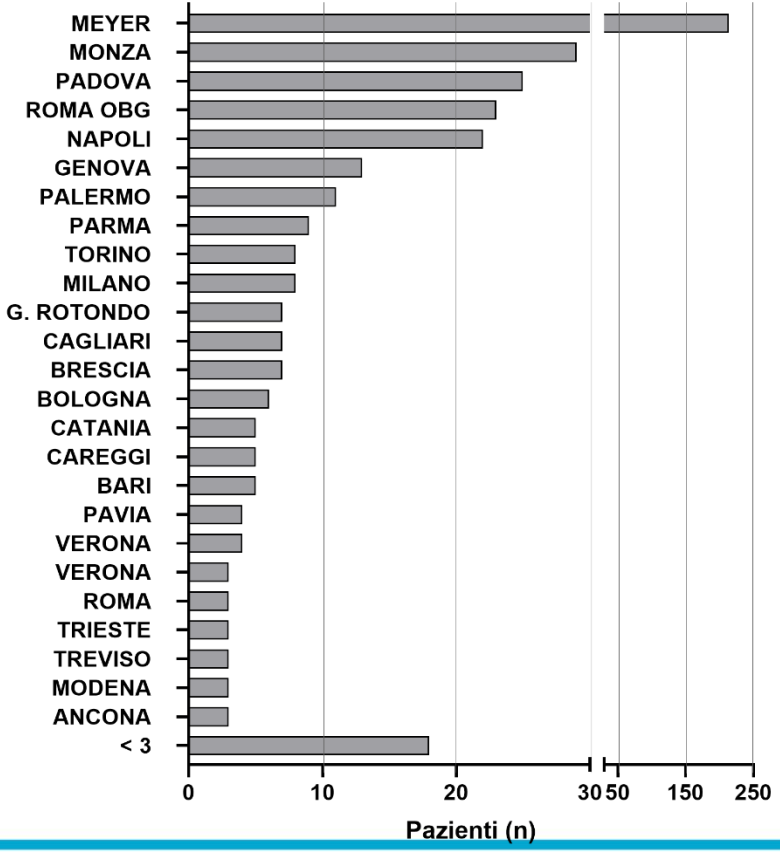


Open questions:

- When and how to stop MAPKi → risk factors for reactivation at MAPKi stop
- How to prevent secondary ND → predictors of seconday ND

ECHO

RICLa, biological study



- **Biopsy**: n=273
- **PB**: n=660 →
  plasma, PBMC, vital cells
- **CSF** (ND-LCH pts): n=120
- **BM** (MS pts, if clinically indicated): n=32 →
  plasma, PMN, mononucleates cells, vital cells

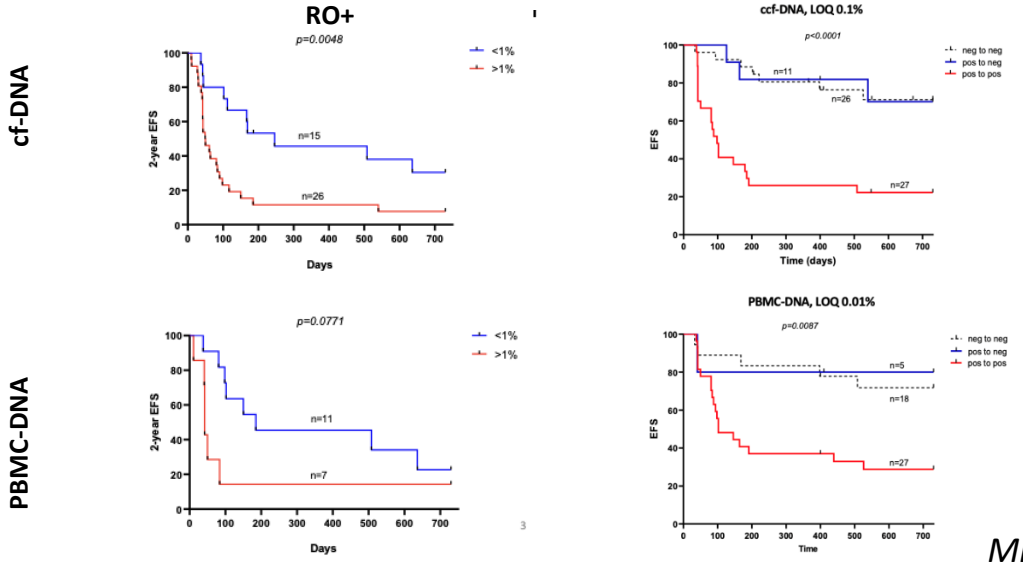
RICLa registration, UPN
Samples specifications: involved sites/ treatment type and time (if applicable)/ disease state (NAD, ADB, ADI, ADW)

Prognostic significance of peripheral *BRAF*^{V600E} in pediatric LCH

PI: E. Sieni

226 children with BRAF V600E+ LCH, at diagnosis and at week 6 after chemo (LCH-IV)

- Braf levels at baseline correlate with 2y EFS
- Persistence of BRAF^{V600E} after 6 weeks of chemotherapy is associated with inferior EFS



Next steps:

- Long-term monitoring of peripheral *BRAF*^{V600E}
- Biological score

Milne P, Beneforti L et al. under review

Meyer Azienda Ospedaliera Universitaria
ECHO

Revised LCH activity criteria scoring system: the ABC score?

- **A**ctivity score (Chairs: A. Barnbrock, Frankfurt and F. Pegoraro, Meyer)
- **B**RAF-related score (Chairs: C. Hutter, St Anna and E. Sieni, Meyer)
- **C**NS-ND score (Chairs: L. Naeije, PMC and T. Greenwood, Karolinska)

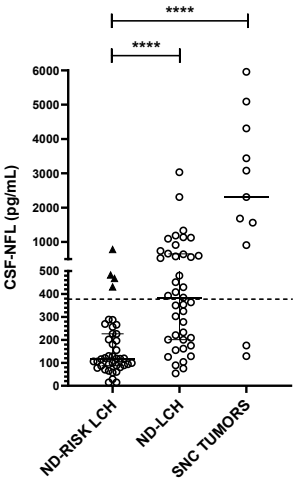
- ECHO project chaired by J.I Henter
- 3 working groups
- Virtual and in presence meetings: next step at the SIOPE meeting in Glasgow

ECHO

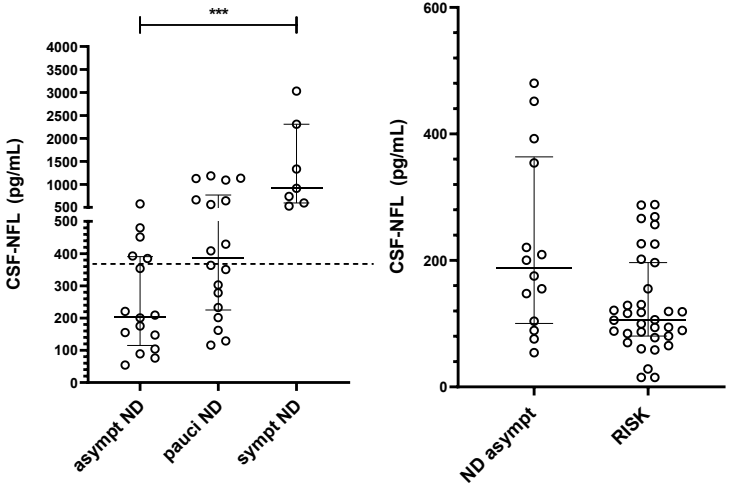
NFL in the CSF and plasma of patients with LCH

Firenze, INT Milano, Padova, OBG Roma, Napoli Paus

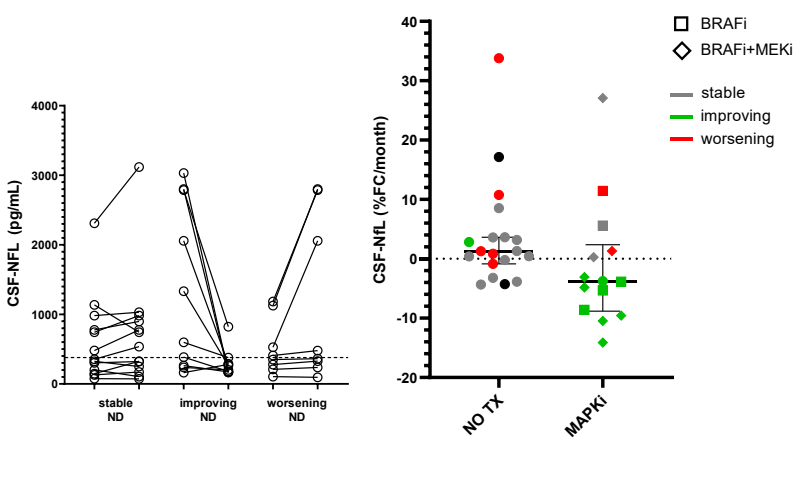
CSF-NFL is increased in ND-LCH patients



CSF-NFL is unable to discriminate pre-symptomatic ND patients



CSF-NFL correlates with ND course

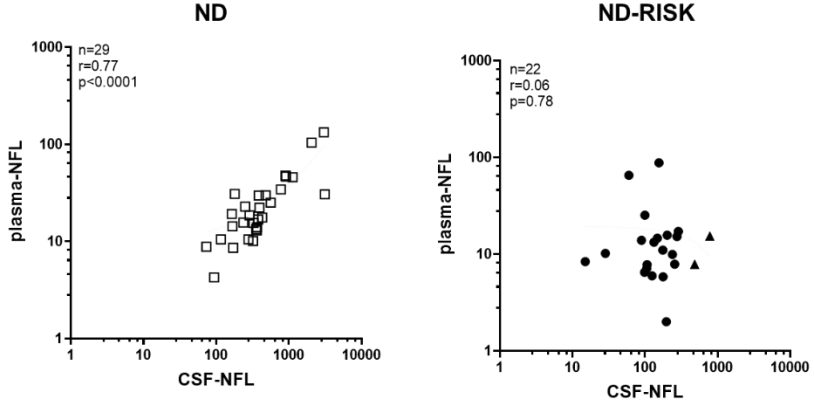


At least one CSF, N=77 (control group: 11 no-LCH CNS tumors)
Longitudinal CSF samples , n=32

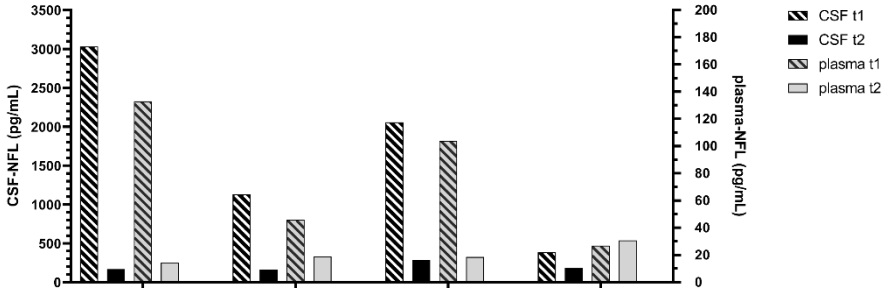
Linda Beneforti, Anita Argentieri et al. in preparation

NFL in the CSF and plasma of patients with LCH

CSF and p-NFL correlation is high in ND patients
N=32 pairs samples



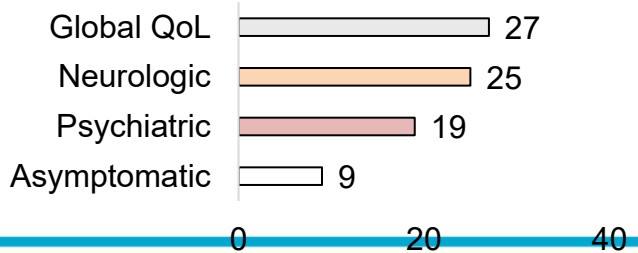
p-NFL mirror CSF-NFL in monitoring response to MAPKi
N=4 patients



Linda Beneforti, Anita Argentieri et al. in preparation

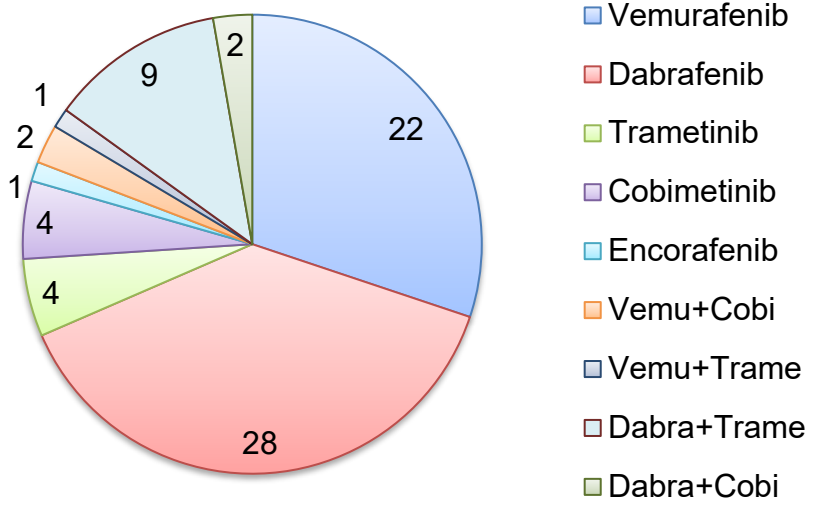
MAPK inhibitors for treating ND-LCH

Age at LCH diagnosis, months – median (IQR)	26 (11-40)
Risk factors – n or n/n tot (%)	
Diabetes insipidus	25 (46)
Cranio-facial bone lesions	36 (67)
Skin	26 (48)
$BRAF^{V600E}$ mutation	50/51 (98)
Time from ND to MAPKi, months – median (IQR)	30 (6-85)
Follow-up since MAPKi initiation, months – median (IQR)	35 (17-67)



N=54

Therapeutic instances



Pegoraro F et al, under review

MAPK inhibitors for treating ND-LCH: results

Florent disability score

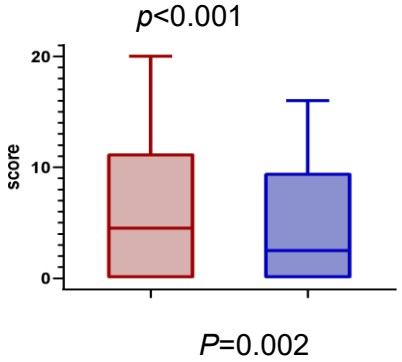
Item	0	1	2	Score
Autonomy/ Independent living	Autonomous/ Independent	Needs minimal or intermittent assistance	Needs permanent assistance	
Weakness	No weakness	Mild weakness, but able to manage normal activities	Not able to have a normal life	
Daily activities	Normal	Slow to complete daily activities	Almost no activity possible	
Social abilities	Normal for age	Some limitation in social interactions	Poor or no social interactions	
School / Work	Able to attend school. Learning delay less than 2 years. Not needing extra help	Able to attend school with some help	Needs to attend "Special" School	
	Able to work without any adaptation	Able to work with adaptation	Not able to work	
Walking	Normal and independent walking	Some unsteadiness but able to walk, with or without support	Needs a wheelchair for daily life	
Speech	Normal	Slow, or slurred but able to communicate	Not able to communicate verbally	
Fine movements	Normal	Some problems with co-ordination	Unable to manage fine movements	
Deglutition/ Swallowing	No difficulty with swallowing	Some problems with swallowing	≥1 episode of aspiration in the last month	
Emotional dysregulation	No signs of dysregulation	Some trouble managing feelings and emotions	Emotional problems causing severe impact on daily life	
Psychiatric symptoms	None	Minor symptoms, manageable in outpatient clinic	Needs hospitalization or permanent anti-psychotics	
Aggressiveness	None	Frequent attacks	Unable to have social contact except with close carers	
Addiction	No	Minor addiction but able to live a normal life	Significant addiction, with daily consumption, impact on life	
Total				

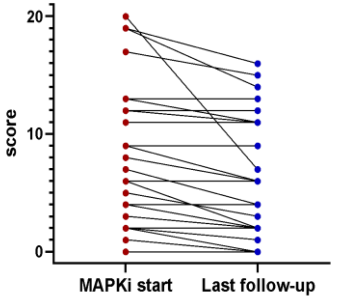
Global QoL

Neurologic

Psychiatric

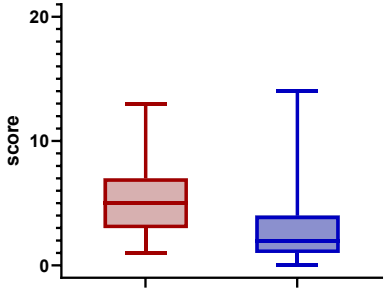
- Clinical response rate was 66% (n=29/44)
- MRI abnormality improvement in 40 patients (74%)
- A composite response was observed in 37 patients (69%)

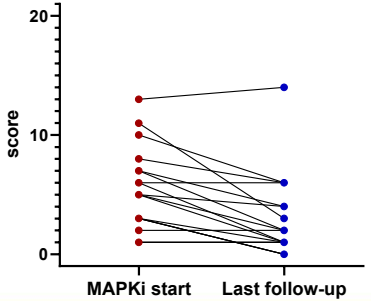




MRI score

	Signal abnormalities				Atrophy and/or Cavitation			
	-	+	++	+++	-	+	++	+++
Dentate nuclei								
Cerebellar white matter								
Cerebellar cortex								
Brainstem								
Basal ganglia and thalamus								
Other brain localizations								





Consensus guidelines on ND-LCH

Key questions

- How to **define** and characterize ND-LCH
- How and whom to **screen** for ND-LCH
- How to **monitor** ND-LCH

Target population

- age <18 years
- with/ at risk of ND-LCH

Target users

- pediatric hemato-oncologists,
- pediatric neurologists, radiologists,
- neuropsychologists,
- biologists

who are committected to patients with LCH

Main topics: disease definition, screening, risk factors, baseline and monitoring evaluations and general recommandations.

Survey results:

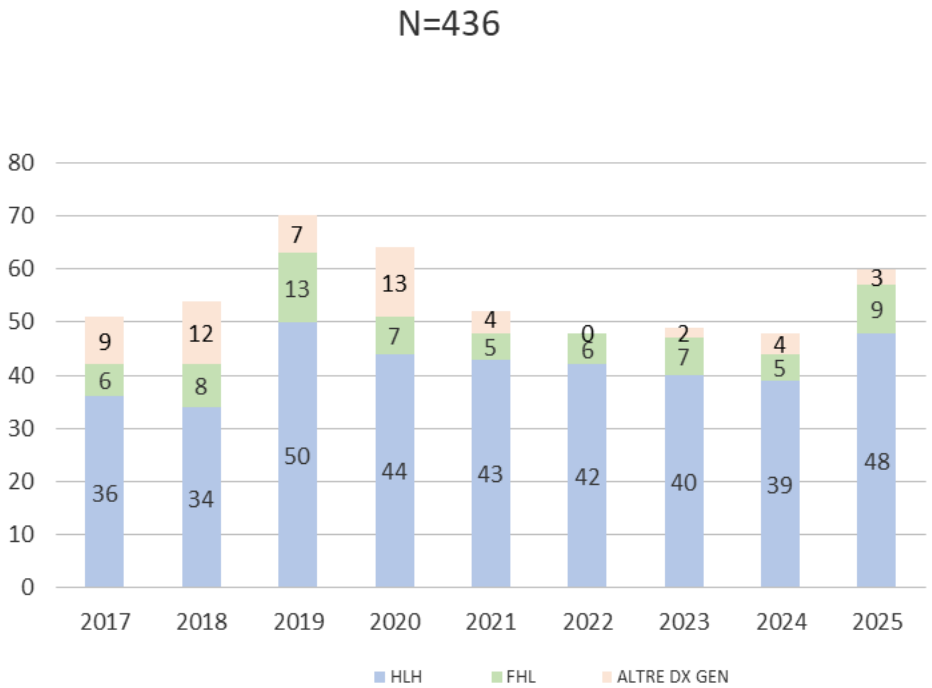
20 /24 (83%) responders

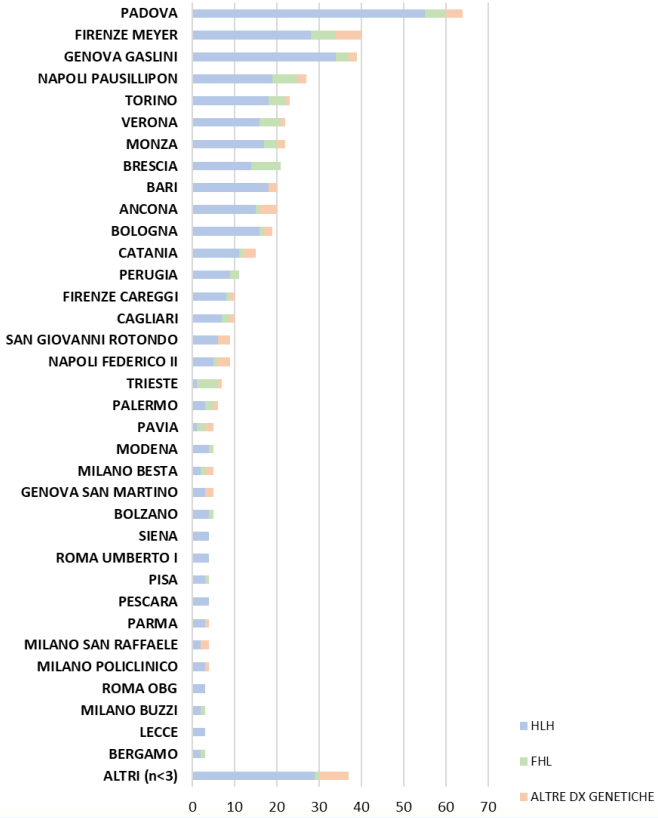
- Strong Consensus: 15 substatements
- Consensus: 15 substatements
- Major agreement: 1 substatement

Prospective validation through the **CNS-LCH Registry** (PI T. Greenwood, co-PI E.Sieni)

ECHO CNS Working group, In preparation

Centralized lab for HLH, Meyer





Meyer IRCCS Azienda Ospedaliera Universitaria

Multi-omics HLH

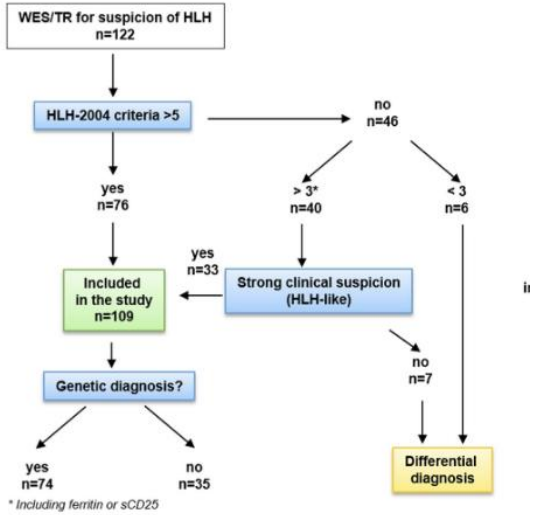
- Studio osservazionale retrospettivo e prospettico
- Approvazione CE in corso
- Finanziamento: Fondazione Meyer, associazione pazienti

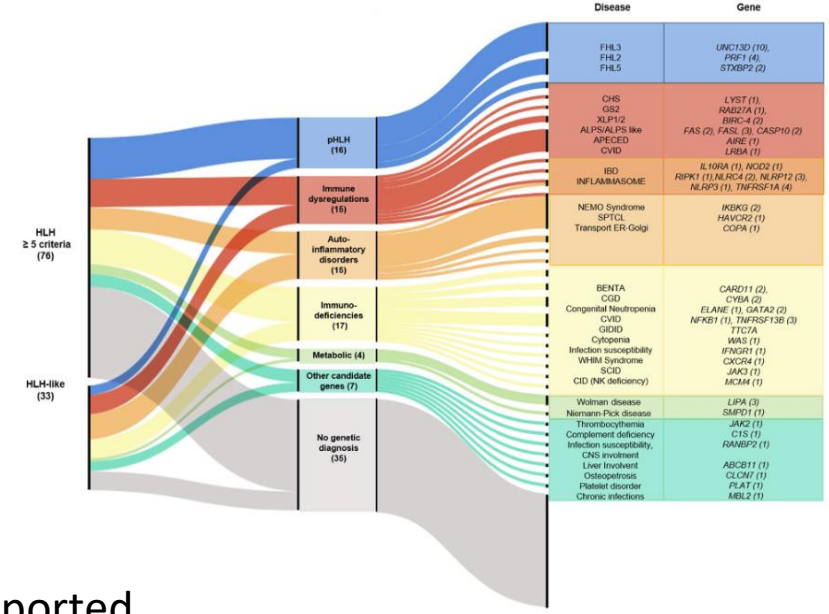
Obiettivo	Endpoints
	Primari
Estensione dello studio funzionale citofluorimetrico	1. Analisi espressione di Perforina, Granzyme B, HLA-DR, CD38, SAP e XIAP su NK; 2. Analisi espressione di CD107a su NK ed NKT DN (test di degranulazione); 3. Analisi TNF-α (test funzionalità proteina XIAP).
Dosaggio delle citochine	Dosaggio delle citochine IL-17A, IL-18, CXCL9 e sCD25 su campioni plasmatici con tecnologia Ella Simple Plex™.
	Secondari
Studio multi-omico volto ad esplorare fattori a) genetici ed epigenetici, b) metagenomici, c) metabolomici e proteomici, in gran parte inesplorati, che contribuiscono allo sviluppo e all'evoluzione della HLH	a) Estensione della ricerca di varianti germinali responsabili della predisposizione allo sviluppo della HLH con approccio Whole Exome Sequencing e analisi dei livelli di metilazione tramite Nanopore Sequencing; b) Monitoraggio del decorso della patologia tramite raccolta di campioni fecali e analisi metagenomica, per identificare i profili microbici associati alla malattia e cambiamenti nella flora batterica. c) Analisi dell'oscillazione dei livelli di metaboliti e proteine tramite raccolta di campioni plasmatici.
Valutazione soglie patologiche	I dati ottenuti ai punti precedenti verranno sottoposti a studi statistici (curve ROC e di event-free survival) per determinare le soglie patologiche nel setting specifico.

BJHaem

Diagnostic impact of exome sequencing in haemophagocytic lymphohistiocytosis: A report from the Italian reference centre

Aurora Chinnici[1,2]
Linda Beneforti[1,2]
Daniela Balasco[1]
Elia Dirupo[3]
Michele Tanturli[4]
Yasmine El Chazli[5]
Alessandra Todesco[6]
Fabio Timeus[7]
Paola Corti[8]
Carmen de Fusco[9]
Annalisa Tondo[1]
Francesco Pegoraro[1]
Elena Sieni[1]
Maria Luisa Coniglio[1]





- Detection rate: 68%, higher than previously reported
- Extensive sequencing is indicated regardless of complete criteria and age

A. Chinnici et al. BJH 2025

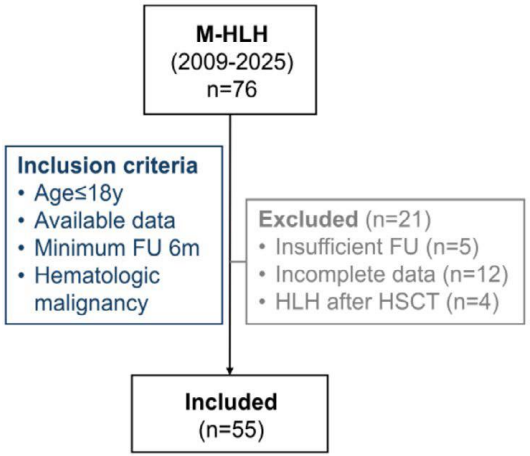
American Journal of Hematology February 2026

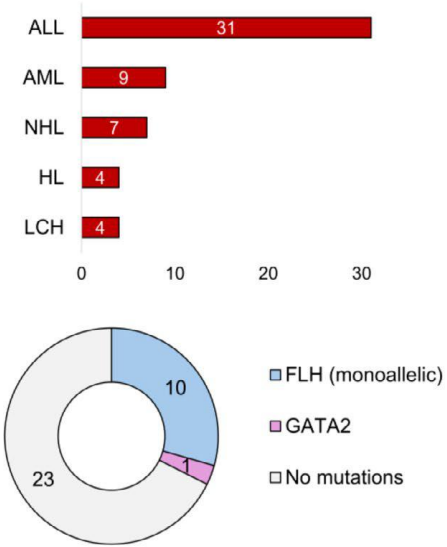
Encouraging Outcomes in Pediatric Malignancy-Associated Hemophagocytic Lymphohistiocytosis: Results From the Italian HLH Registry

Francesco Pegoraro[1,2] | Irene Ferri[2] | Aurora Chinnici[2] | Linda Beneforti[2,3] | Irene Trambusti[2] | Simona Gobbi[4] | Rosa Maria Daniele[5] | Rosamaria Mura[6] | Elena Palmisani[7] | Marco Zecca[8] | Giulia Albrici[9] | Alessandra Todesco[10] | Carmela De Fusco[11] | Samuele Naviglio[12] | Veronica Barat[13] | Fabio Timeus[14] | Marta Pillon[10] | Carmelo Rizzari[15] | Annalisa Tondo[2] | Maria Luisa Coniglio[2] | Elena Sieni[2]

HLH Registry data, inclusion criteria:

- HLH-2004 criteria
- hematologic malignancies



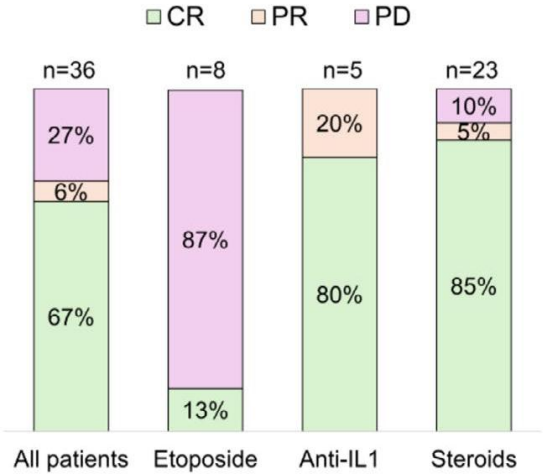


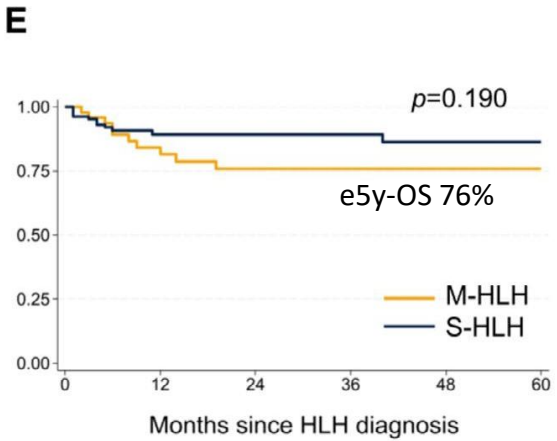
F. Pegoraro, I. Ferri et al. AJH 2026

American Journal of Hematology February 2026

Encouraging Outcomes in Pediatric Malignancy-Associated Hemophagocytic Lymphohistiocytosis: Results From the Italian HLH Registry

ORR: 70%
HLH reactivation 9%
HSCT (85%), in most cases due to malignancy





F. Pegoraro et al. AJH 2026

HLH in sibling pairs

TRANSPLANTATION Blood, 2008

Treatment dilemmas in asymptomatic children with primary hemophagocytic lymphohistiocytosis

Giovanna Lucchini,[1] Rebecca Marsh,[2] Kimberly Gilmour,[1] Austen Worth,[1] Zohreh Nademi,[3] Anupama Rao,[4] Claire Booth,[1] Persis Amrolia,[1] Juliana Silva,[1] Robert Chiesa,[1] Robert Wynn,[5] Kai Lehmberg,[6] Itziar Astigarraga,[7] Tayfun Güngör,[8] Jan Stary,[9] Despina Moshous,[10] Marianne Ifversen,[11] Daniel Zinn,[12] Michael Jordan,[2] Ashish Kumar,[2] Takahiro Yasumi,[13] Paul Veys,[1] and Kanchan Rao[1]

- To expand the published cohort and fup
- To search for specific genotype-phenotype correlations
- To monitor for late complications after HCT

Giovanna Lucchini, Violante Gustuti (Monza)

Participating centres:

Czech Republic, France, Germany, Italy, Japan, Spain, Switzerland, United Kingdom, USA

- Italy: Firenze, Padova, Genova, Napoli Paus

Inclusion criteria:

- pHLH (FHL2, FHL3, FHL4, FHL5, GS2)
- Age < 18y
- At least 2 siblings/cousins with the same genetic mutation: index case and asymptomatic case

HLH in sibling pairs

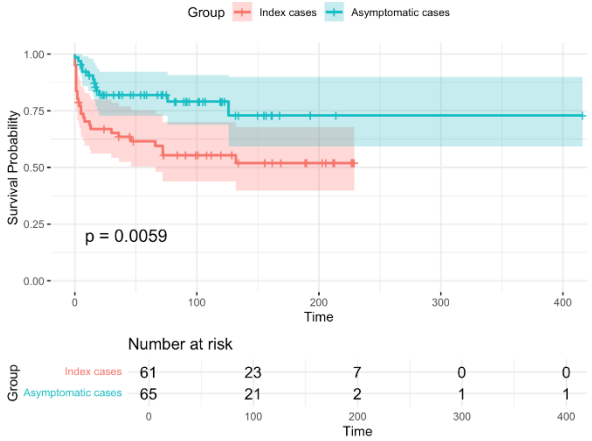
Total responses
N=132

Excluded
N=5

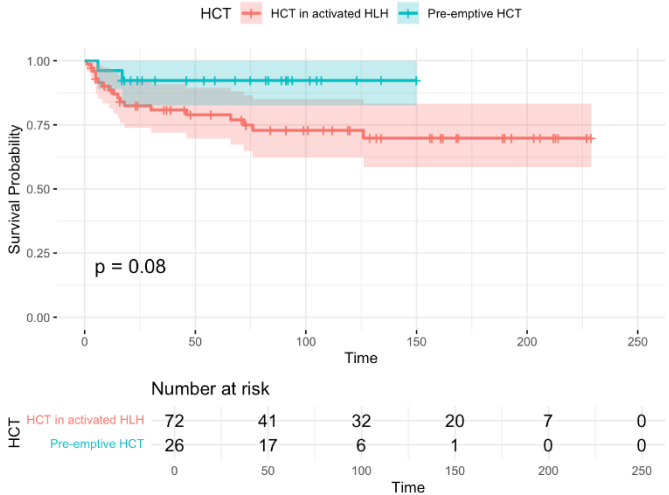
Enrolled
N=127

- Index cases (ICs) n=61
- Asymptomatic cases (ACs) n=65
- 57 couples,3 triplets,1 quadruplet

- Overall HLH activation: n = **96/127 (76%)**
- Among "Asymptomatic cases"(ACs), **34/65 cases (52%)**
  Median age at HLH activation: 6 months (0-192)
- 26/34 (76,5%) difference in age of activation < 36 months



ACs: 5-year OS 82% (95% CI: 73-92%)
ICs: 5-year OS 62% (95% CI: 50-65%)

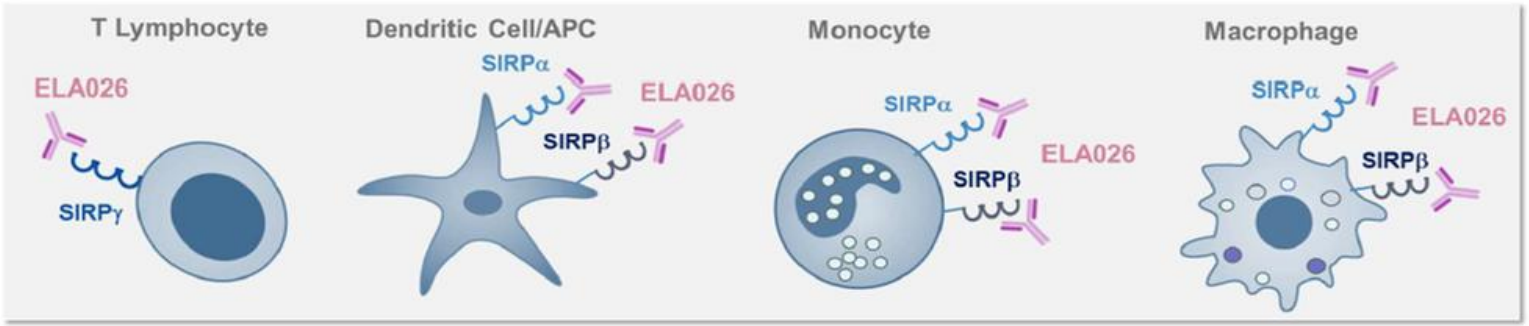


HCT after overt HLH : 5-yr OS **79%** (95% CI 70-89%)
Pre-emptive HCT: 5-yr OS **92%** (95% CI 82-100%)

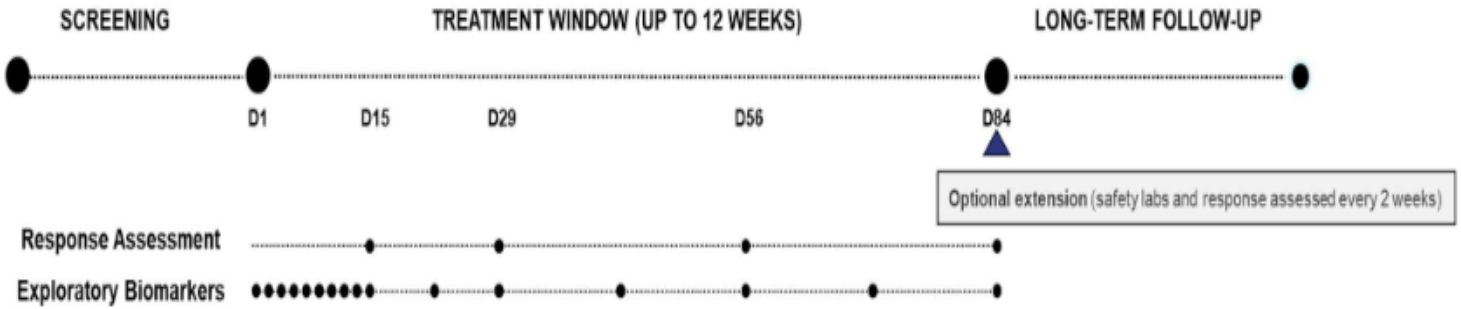
the SURPASS Phase 2/3 Pivotal Study of ELA026 in Secondary Hemophagocytic Lymphohistiocytosis (sHLH)

ELECTRA THERAPEUTICS

- A phase 2/3, open-label, single-arm, multicenter study
- ELA026 is a fully human, monoclonal antibody targeting signal regulatory proteins (SIRP)α, SIRPβ1 on myeloid cells and SIRPγ on activated T cells



STUDY SCHEME



Cohort A: mHLH ≥18 years old, treatment naïve.

Cohort B: non-mHLH subtypes ≥18 years old and **any sHLH type 6 to 17 y (US), 15-17 y (EU),** treatment naïve.

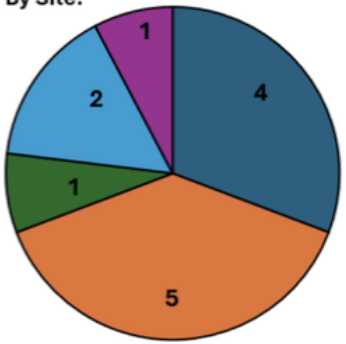
Exclusion criteria: patients enrolled in other therapeutical clinical trials

SURPASS Study Updates

Enrollment Updates

14 Total Patients Enrolled

By Site:



- MD Anderson/ Dr. Iyer
- Memorial Sloan Kettering/Dr. Horwitz
- University of Alabama/ Dr. Goyal
- University College of London/ Dr. Gohil
- University of Utah/ Dr. Shah

By Country:
United States: 12
United Kingdom: 2

By Cohort:
Cohort A: 10
Cohort B: 4

Activation Updates

29 / 35 sites are active in USA, UK, Italy, Netherlands and Spain

AIEOP centres:

- Florence
- Genoa
- Monza
- Trieste

Use of ruxolitinib for patients with hyperinflammatory syndromes – A real-world experience study

Broad study population: FHL, HLH, HLH-like, hyperinflammatory syndromes

REDCAP database

St. Jude Children's Research Hospital
Finding cures. Saving children.

IRCCS Meyer
Azienda Ospedaliero Universitaria

Agreement Sr Jude and Meyer, March 2026

- Coordination EU enrollment
- CRF simplification
- Focus on FHL

Preliminary survey, FHL

	N
Firenze	4
Napoli	3
Trieste	2
Brescia	1
Verona	2
Monza	1

Meetings

In 2025

- Histiocyte Society Meeting, Seattle,2025
- ECHO session at SIOPE 2025
- Riunione GdL 28/2/2025

Next…

- SIOPE 2026, Glasgow
  ECHO session May 14
  BRAF tumors- ECHO&ITCC session on May 15

- Riunione Gruppo di Lavoro, Firenze: June 2026

- Histiocyte Society Meeting, Rotterdam 2026

Thank you

Gruppo di lavoro istiocitosi:

Stefano Chiaravalli, INT Milano

Paola Corti, Monza

Carmen De Fusco, Napoli Paus

Stefania Gaspari, OBG Roma

Concetta Micalizzi, Gaslini, Genova

Alessandra Todesco, Padova

Nino Trizzino, Palermo

Anna Maria Buccoliero, Firenze

Emanuela Passoni, Policlinico Milano

e tutti i partecipanti agli studi e alle riunioni!

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