Emapalumab in the Treatment of Adult Patients with Malignancy-Associated Hemophagocytic Lymphohistiocytosis (mHLH)

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ABSTRACT

Purpose: Interferon gamma (IFNγ) activity has a key role in the pathogenesis of hemophagocytic lymphohistiocytosis (HLH). This study aimed to evaluate the efficacy, safety, and pharmacodynamics (PD) of emapalumab, a fully human IgG1 anti-IFNγ monoclonal antibody, in patients who met the HLH-2004 diagnostic criteria, did not have primary HLH and had not received prior HLH treatment (except glucocorticoids). **Methods:** Seven adults with malignancy-associated HLH (mHLH) were administered emapalumab before this study (NCT03985423) was prematurely terminated by the sponsor for non-safety reasons. The optimized HLH inflammatory (OHI) index was retrospectively determined in all patients. A complete response (CR) was defined as resolution of fever, splenomegaly, cytopenias, hyperferritinemia, and any coagulopathy, plus no sustained worsening of soluble CD25 (sCD25; also known as soluble interleukin-2 receptor α) levels at Week 4 (or end of treatment [EOT], if earlier). A partial response (PR) was defined as a >50% improvement in ≥3 of these biomarkers. **Results:** All patients received chemotherapy and 6 patients were receiving glucocorticoids prior to study entry. All patients received ≥1 dose of emapalumab (median, 7 [range, 1–36]). Median duration of treatment was 20 (range, 1–123) days. All patients prematurely discontinued emapalumab (withdrew consent [n=2], death [n=2], adverse event [n=1], physician decision [n=1], lack of insurance/citizenship [n=1]). Per-protocol (PP) and investigator-assessed (PI) responses (all PRs) were seen in 2/6 (33%) and 4/6 (67%) patients, respectively. Glucocorticoid dose was reduced by ≥50% by EOT in all 4 patients with a PI response. Reductions in chemokine C-X-C motif ligand 9 (CXCL9) and sCD25 levels from baseline were associated with PP and PI response. PI response was closely associated with OHI index status evolution from positive to negative. **Conclusion:** PI response to emapalumab correlated with improvements in HLH biomarkers and evolution of OHI index status. OHI index status may provide an alternative objective measure of treatment effect in adults with mHLH.

INTRODUCTION

- Malignancy underlies approximately half of all cases of hemophagocytic lymphohistiocytosis (HLH) in adults[1]
- Outcomes of patients with malignancy-associated HLH (mHLH) are poor, with median survival of ~2 months and 1-year survival of <20%[1]
- The optimized HLH inflammatory (OHI) index (soluble CD25 [sCD25] >3900 U/mL and ferritin >1000 ng/mL) was recently proposed as a more specific method of diagnosing HLH in patients with malignancies compared with conventional HLH-2004 criteria[2]
- Interferon gamma (IFNγ) plays a key role in the pathogenesis of HLH,[3] with serum IFNγ levels being correlated with HLH disease activity[4]
- Emapalumab binds and neutralizes IFNγ, and is approved for the treatment of patients with primary HLH with refractory, recurrent or progressive disease, or intolerance to conventional HLH therapy[5]
  - Emapalumab has also demonstrated efficacy and safety in patients with macrophage activation syndrome, a form of secondary HLH, in patients with Still's disease (systemic juvenile idiopathic arthritis or adult-onset Still's disease)[6]

OBJECTIVES

- This study (Clinicaltrials.gov identifier: NCT03985423) aimed to evaluate the efficacy, safety, and pharmacodynamics of emapalumab in adults with mHLH

METHODS

Study design

- Adult patients (aged ≥18 years) who met the HLH-2004 diagnostic criteria[7] and did not have primary HLH were enrolled in this study
  - Patients must not have received prior treatment for HLH (except glucocorticoids)
- Eligible patients were administered a loading dose of emapalumab (6 mg/kg intravenously [IV]), followed by maintenance doses (3 mg/kg IV) every 3 days for 2 weeks, then twice weekly until a clinically satisfactory response was achieved

Endpoints

- **Primary endpoint:** Per-protocol (PP) complete response (CR) or partial response (PR) at Week 4 (or end of treatment [EOT], if earlier)
  - CR was defined as resolution of fever, splenomegaly, cytopenias, hyperferritinemia, and any coagulopathy, plus no sustained worsening of sCD25 levels
  - PR was defined as a >50% improvement in ≥3 biomarkers listed in the CR definition
- **Secondary endpoints:** Included best response on treatment and overall response rate (ORR) at EOT
- Other efficacy endpoints included PR as per-investigator (PI) response
- **Pharmacodynamic endpoints:** Chemokine C-X-C motif ligand 9 (CXCL9), a recognized marker of IFNγ activity, and other relevant biomarkers (e.g., soluble CD25 [sCD25], ferritin, platelet counts)
- Treatment-emergent adverse events (TEAEs) were also recorded, including infusion-related reactions and anti-drug antibodies (ADAs)

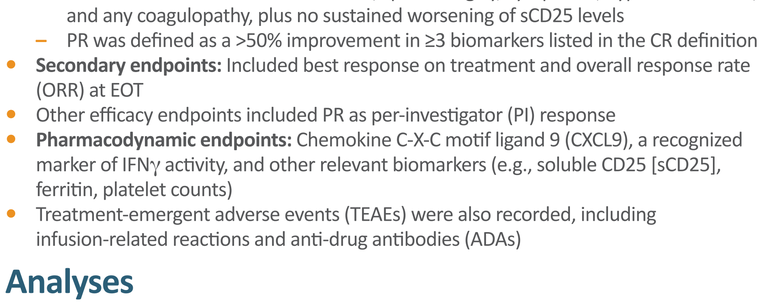
Analyses

- OHI index was determined retrospectively
- Univariate pharmacodynamic association analyses investigating the relationship between biomarker levels and response to emapalumab were performed on all patients with available biomarker (laboratory and inflammatory marker) data at baseline and at subsequent timepoints through to EOT or discontinuation
- Missing baseline biomarker data were imputed using first observation carried backwards

RESULTS

- Seven adults with mHLH were administered emapalumab (median number of doses, 7 [range, 1–36]) before this study was prematurely terminated by the sponsor for non-safety reasons (**Figure 1**)
  - One patient did not have post-baseline data because of early study discontinuation
- All patients prematurely discontinued emapalumab (**Figure 1**)

Figure 1: Patient disposition



Baseline characteristics

- Baseline characteristics of patients participating in this study are provided in **Table 1**
  - All patients had an underlying hematologic malignancy and had received chemotherapy prior to study enrollment
    - One patient continued to receive daily etoposide for the underlying hematologic malignancy
  - One patient had a negative OHI index status at baseline
- All patients had received glucocorticoids for mHLH prior to or at study entry, and continued glucocorticoid therapy for the duration of the study

Table 1: Patient demographics and baseline characteristics

Characteristic	N=7
Age, years, median (range)	50 (25–73)
Sex, male, n (%)	4 (57.1)
Race, n (%)	
White	4 (57.1)
Other	3 (42.9)
Malignancy, n (%)	
Lymphoma	4 (57.1)
Acute leukemia	3 (42.9)
Positive OHI index status, n (%)	6 (85.7)

OHI, optimized hemophagocytosis lymphohistiocytosis inflammatory

Response to emapalumab

- PP and PI responses (all PRs) were observed in 2/6 (33%) and 4/6 (67%) patients, respectively, after administering emapalumab (**Table 2**)
- Among the 4 patients with a PI response:
  - Glucocorticoid dose was reduced by ≥50% by EOT in all 4 patients
  - One patient proceeded to hematopoietic stem cell transplant

Table 2: Response rates at Week 4/EOT by PP and PI

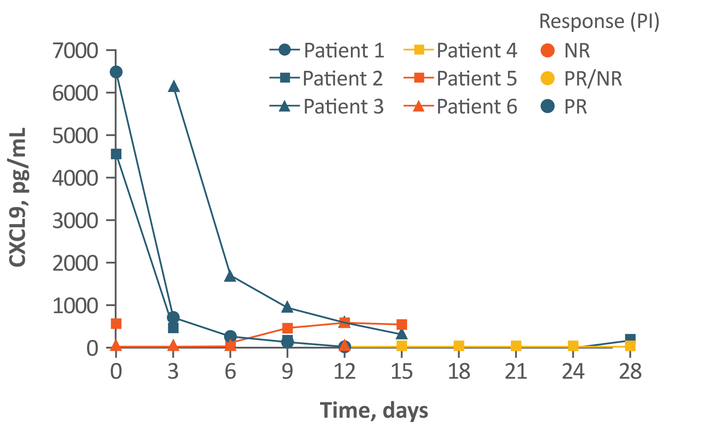
	PP response (N=6)	PI response (N=6)
ORR, n (%)	2 (33)	4 (67)
CR, n (%)	0	0
PR, n (%)	2 (33)	4 (67)
No response, n (%)	4 (67)	2 (33)

CR, complete response; EOT, end of treatment; ORR, overall response rate; PI, per-investigator assessment; PP, per-protocol; PR, partial response

Biomarker analyses

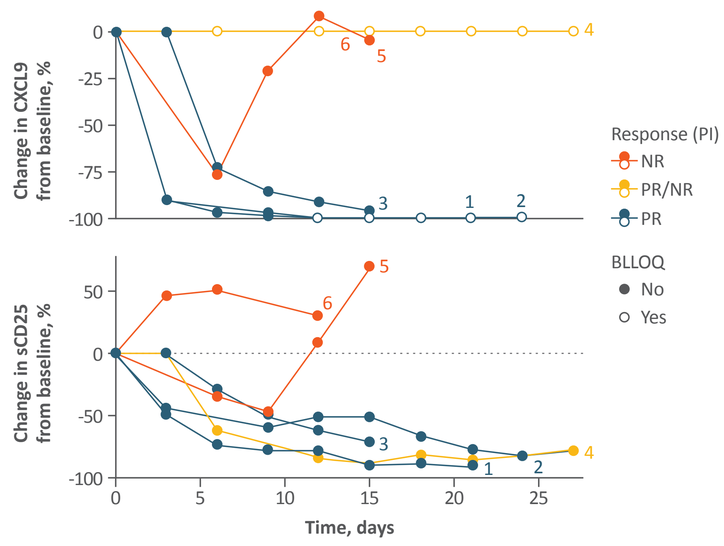
- No association was observed between baseline biomarker values and response to emapalumab in a univariate predictive analysis
- CXCL9 and sCD25 levels were substantially reduced from baseline in patients with mHLH who had a PI PR following emapalumab administration (**Figures 2 and 3**)

Figure 2: CXCL9 levels in patients with mHLH administered emapalumab



CXCL9, chemokine C-X-C motif ligand 9; mHLH, malignancy-associated hemophagocytic lymphohistiocytosis; NR, no response; PI, per-investigator assessment; PR, partial response; PR/NR, initial partial responder who subsequently lost response

Figure 3: Percent change in CXCL9 and sCD25 levels from baseline in patients with mHLH administered emapalumab

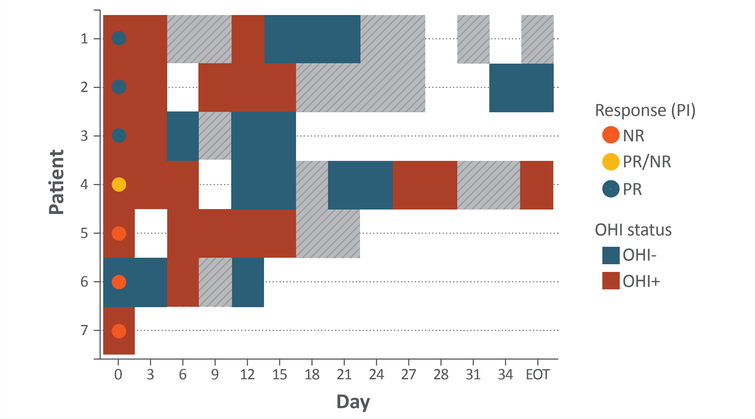


Missing baseline values were imputed by FOCB.
BLLOQ, below lower limit of quantification; CXCL9, chemokine C-X-C motif ligand 9; FOCB, first observation carried backwards; mHLH, malignancy-associated hemophagocytic lymphohistiocytosis; NR, no response; PI, per-investigator assessment; PR, partial response; PR/NR, initial partial responder who subsequently lost response; sCD25, soluble CD25

OHI index evolution

- PI response was closely associated with OHI index status evolution from positive to negative (**Figure 4**)

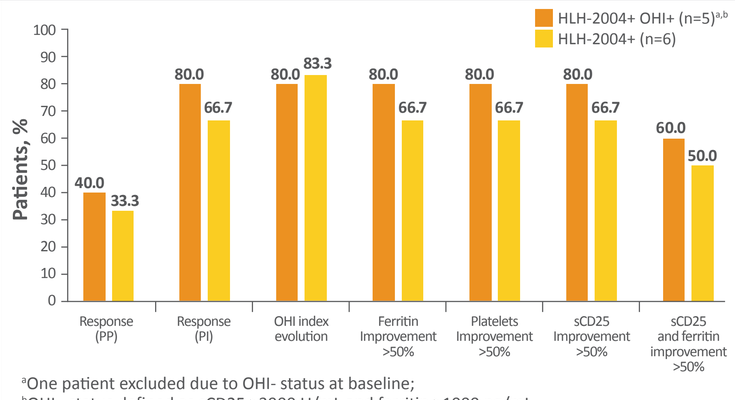
Figure 4: PI response assessments and OHI index evolution over time



Missing baseline values were imputed by FOCB. White box = missed visit; grey hashed box = missing data.
FOCB, first observation carried backwards; NR, no response; OHI, optimized hemophagocytic lymphohistiocytosis inflammatory index; PI, per investigator assessment; PR, partial response; PR/NR, initial partial responder who subsequently lost response

- The majority of patients who responded to emapalumab based on OHI status, PP response, and PI assessment also had ≥50% improvement in HLH-specific biomarkers (**Figure 5**)

Figure 5: Response rates by OHI index status at baseline



[a]One patient excluded due to OHI- status at baseline;
[b]OHI+ status defined as sCD25 >3900 U/mL and ferritin >1000 ng/mL.
AST, aspartate aminotransferase; HLH, hemophagocytic lymphohistiocytosis; mHLH, malignancy-associated hemophagocytic lymphohistiocytosis; OHI, optimized hemophagocytic lymphohistiocytosis inflammatory; PI, per-investigator assessment; PP, per-protocol; sCD25, soluble CD25

Safety

- All patients reported at least one TEAE, the majority of which were mild in severity (**Table 3**)
  - Five (71.4%) patients experienced serious TEAEs
  - Two patients discontinued study drug due to TEAEs (hepatitis, human herpesvirus 6 encephalitis, and fatal progression of acute myeloid leukemia [all serious; n=1]; and fungemia and pulmonary hemorrhage [not serious; n=1])
- Four (57.1%) TEAEs were fatal (acute myeloid leukemia, lymphoma, bacteremia, and sepsis)
- No study drug-related TEAEs or infusion-related reactions were reported
- No ADAs were observed

Table 3: Overall summary of TEAEs

n (%)	N=7
Any TEAEs	7 (100)
TEAEs by severity	
Mild	7 (100)
Moderate	3 (42.9)
Severe	5 (71.4)
Any drug-related TEAE	0
Any serious TEAE	5 (71.4)
Any TEAE leading to trial drug discontinuation	2 (28.6)
Any TEAE resulting in death	4 (57.1)

TEAE, treatment-emergent adverse event

CONCLUSIONS

- Four out of 6 evaluable patients with mHLH demonstrated a PR by PI when administered emapalumab, a monoclonal antibody that binds and neutralizes IFNγ
- PI response to emapalumab correlated with substantial improvements on CXCL9, sCD25, ferritin, and platelet levels, with complete normalization in some cases
- Of the 5 evaluable patients with OHI+ status at baseline, 4 had a PR by PI and a complete resolution of OHI parameters at one point during the treatment course
  - PI response corroborated well with evolution of OHI index status, offering a potential alternative objective measure for assessing treatment effect in adults with mHLH
- However, no firm conclusions can be made from the available data because of the early discontinuation of this study and small patient numbers

REFERENCES

1. Lee C, Logan AC. *Cancers (Basel)* 2023;15:1839; 2. Zoref-Lorenz A, et al. *Blood* 2022;139:1098–1110;
3. De Benedetti F, et al. *Nat Rev Rheumatol* 2021;17:678–691; 4. Daver N, et al. *Cancer* 2017;123:3229–3240;
5. GAMIFANT® (emapalumab-lszg). US prescribing information. 2024;
6. De Benedetti F, et al. *Ann Rheum Dis* 2023;82:857–865. 7. Henter JI, et al. *Pediatr Blood Cancer* 2007;48:124–131.

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DISCLOSURES

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