Emapalumab is associated with rapid and sustained benefits in pHLH subgroups, including CNS involvement and previously untreated patients: Analysis of trials NI-0501-04, NI-0501-05 and NI-0501-09

A092

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*At time of analysis completion.

CONCLUSIONS

- **Emapalumab provides substantial efficacy across primary hemophagocytic lymphohistiocytosis (pHLH) subgroups based on the investigator assessment.**
- **Outcomes were comparable in previously untreated and previously treated cohorts, underscoring emapalumab's potential utility irrespective of the line of therapy.**
- **A high proportion of central nervous system (CNS)-positive patients responded and reached hematopoietic stem-cell transplantation (HSCT) or maintained a durable response.**
- **These pooled data reinforce interferon-γ (IFNγ) neutralization with emapalumab as a strategy that achieves high response rates irrespective of CNS status or prior therapy.**

INTRODUCTION

- Emapalumab is a fully human IgG1 anti-IFNγ monoclonal antibody that binds both free and receptor-bound IFNγ, neutralizing its biological activity.[1]
- It is approved by the US Food and Drug Administration for adults and children with pHLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy.[2]
- However, data are limited in patients without prior HLH treatment and involvement of CNS on outcomes with emapalumab.
- This post-hoc exploratory analysis provides additional insights into treatment with emapalumab in pHLH using an expanded pooled dataset that assessed treatment responses based on CNS involvement and prior HLH treatment.

OBJECTIVES

- The key objectives of this post-hoc exploratory analysis were to compare, by prior HLH treatment status (previously untreated vs previously treated) and baseline CNS involvement status (CNS involved vs not involved):
  - i. Investigator-assessed overall response (OR=complete response [CR] + partial response [PR]) at Week 8 or end-of treatment (EOT) and best OR up to Week 8 or end of treatment (EOT)
  - ii. Time to first investigator-assessed response, and
  - iii. Bridging-success survival, defined as survival to allogeneic HSCT or alive ≥3 months post-EOT without HSCT.

METHODS

Study Design

- Individual patient data were pooled from studies NI-0501-04 (n=45),[3] its long-term follow-up study NI-0501-05 (n=37 of 45 in NI-0501-04),[4] and NI-0501-09 (n=35).[5] A total of 80 patients from these studies were included in this analysis.

Patient Population

- Total evaluable set (n=73): 7 patients excluded from the post-hoc exploratory analysis (5 patients received < 3 doses of emapalumab and 2 patients were protocol violations).
- Response-evaluable set (n=62): Patients who received ≥3 emapalumab doses and had a recorded investigator assessment at Week 8 or EOT.
- Best response-evaluable set (n=71): Patients who received ≥3 emapalumab doses and had a recorded investigator assessment up to Week 8 or EOT.

Treatment Response and Statistical Analysis

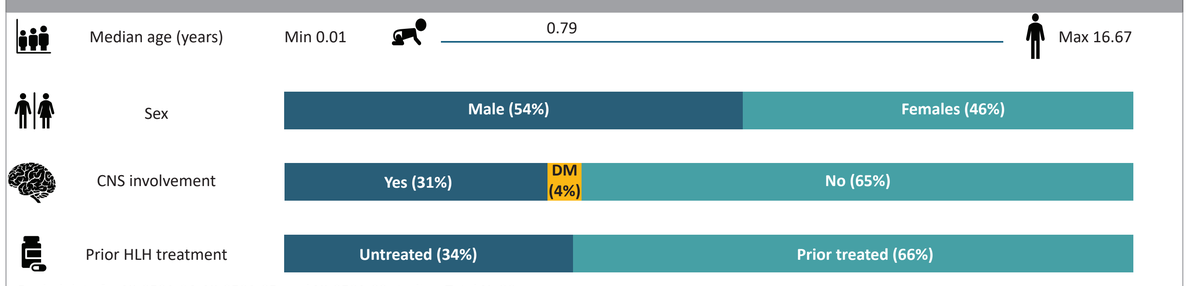
- To reflect real-world clinical practice, instead of protocol definitions, responses were evaluated using the treating investigator's global assessments and classified as
  - CR (complete response or non-active disease)
  - PR (partial response or HLH improvement)
  - OR (CR + PR) or
  - No response (NR; progressive disease, reactivation, worsening or death).
- Absolute risk differences (RD) in bridging-success survival were accompanied by two-sided 95% confidence intervals (CI) calculated with the Fisher's exact test and Fisher's exact *p* values (α=0.05).

RESULTS

Demographics and Baseline Characteristics

- Key demographics and baseline characteristics of the patients included in the pooled analysis are presented in **Figure 1.**

Figure 1: Baseline characteristics of patients included in the pooled analysis

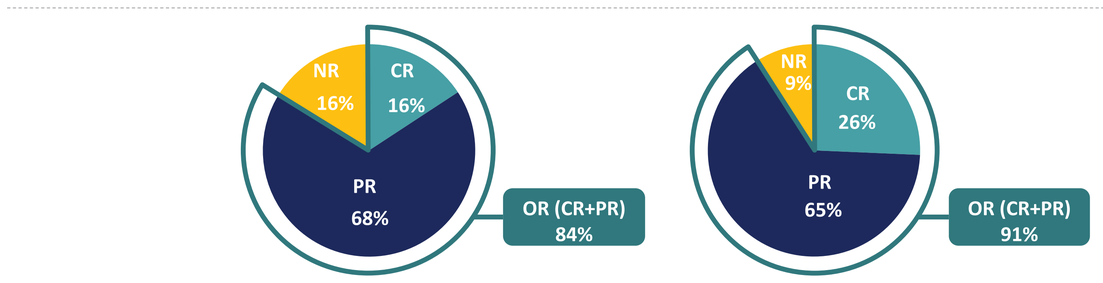


Pooled data for NI-0501-04, NI-0501-05, and NI-0501-09 studies. Total N=80.
CNS, central nervous system; DM, data missing; HLH, hemophagocytic lymphohistiocytosis.

Analysis Based on CNS Involvement

- Based on the investigator's assessment, patients without CNS involvement had higher CR rates than those with CNS involvement, yet both had an OR >80% in these studies **(Figure 2).**

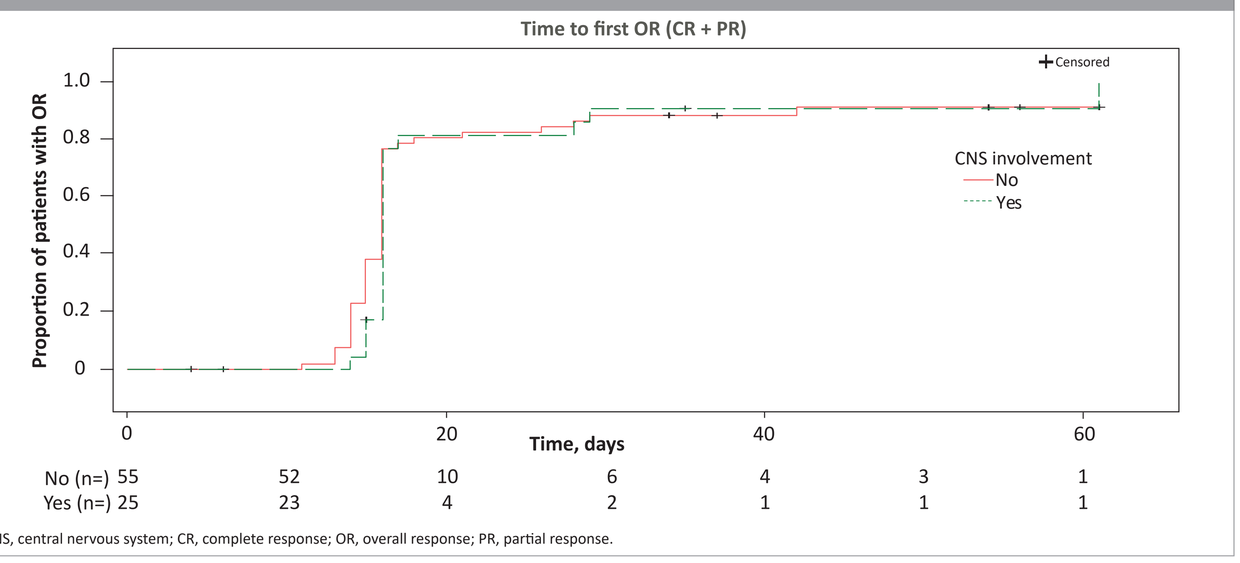
Figure 2: At week 8 or end of treatment, most patients with CNS involvement (84%) responded to emapalumab



*5 patients received <3 doses of emapalumab, 2 were protocol violations, and 11 without investigator assessed response at Week8/EOT and/or missing baseline CNS status.
CNS, central nervous system; CR, complete response; NR, no response; OR, overall response; PR, partial response.

- Best OR rates up to Week 8/EOT as assessed by the investigator were 91% and 96% in the CNS-positive and CNS negative groups, respectively.
- Time to achieving first OR (16 days) was similar between those with or without CNS involvement **(Figure 3)**.

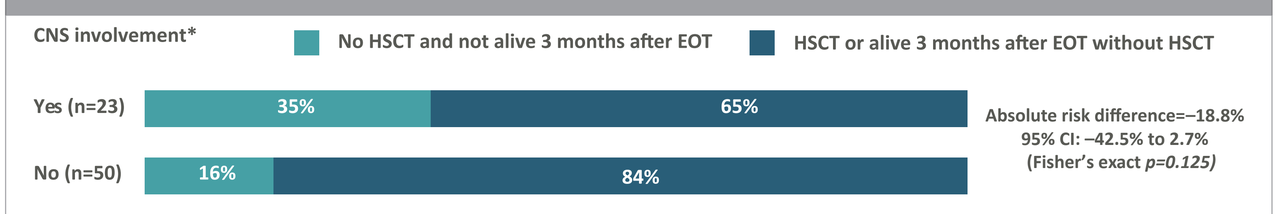
Figure 3: CNS involvement at baseline did not affect the time to first investigator-assessed overall responses



CNS, central nervous system; CR, complete response; OR, overall response; PR, partial response.

- The survival rate to HSCT or ≥3 months post-EOT was higher among patients without baseline CNS involvement vs. those with baseline CNS involvement. However, this difference was not statistically significant **(Figure 4)**.

Figure 4: Patients without CNS involvement showed a trend towards higher survival rate to HSCT or ≥3 months post-EOT

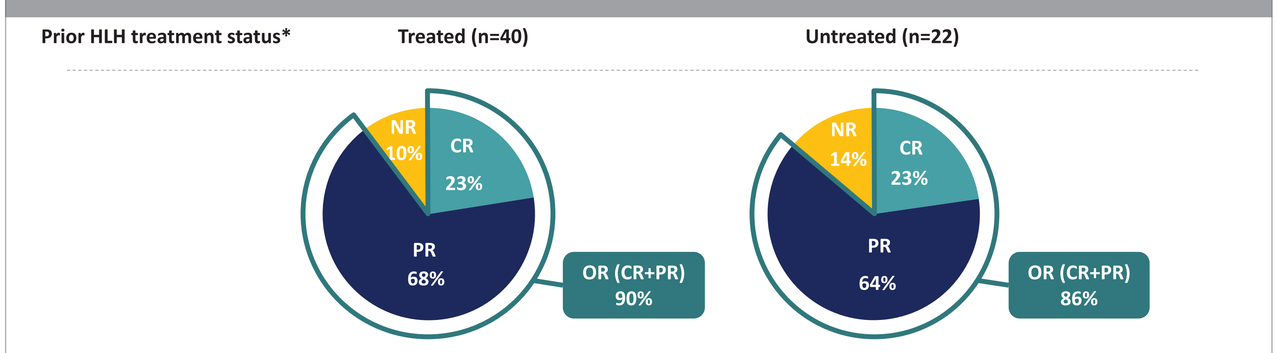


*5 patients received <3 doses of emapalumab, 2 were protocol violations.
CI, confidence interval; CNS, central nervous system; EOT, end of treatment; HSCT, hematopoietic stem-cell transplantation.

Analysis Based on Prior Treatment

- Based on the investigator's assessment, the overall response was high irrespective of prior HLH treatment status **(Figure 5)**.

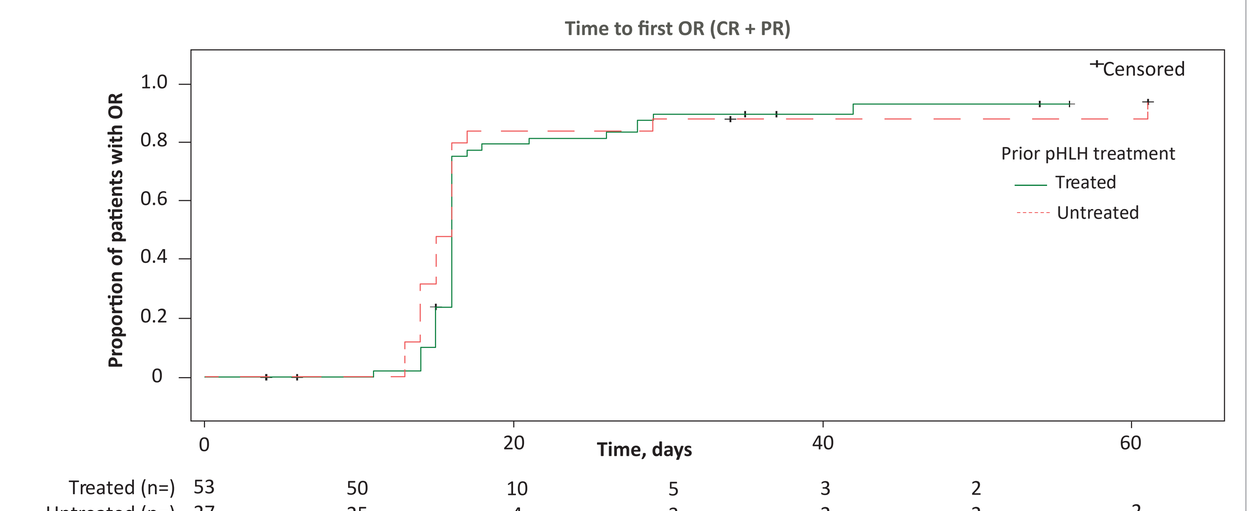
Figure 5: At Week 8/EOT, overall response rates were comparable in both previously treated and untreated patients



*5 patients received <3 doses of emapalumab, 2 were protocol violations, and 11 without investigator assessed response at Week 8/EOT.
CR, complete response; EOT, end of treatment; NR, no response; OR, overall response; PR, partial response.

- Best OR rates were similar in previously treated and untreated patients (94% [CR 34%] and 96% [CR, 29%], respectively).
- The time to first investigator-assessed responses were comparable across both first- and second-line of therapy (15 and 16 days, respectively); similar high outcome rates for OR were observed **(Figure 6)**.

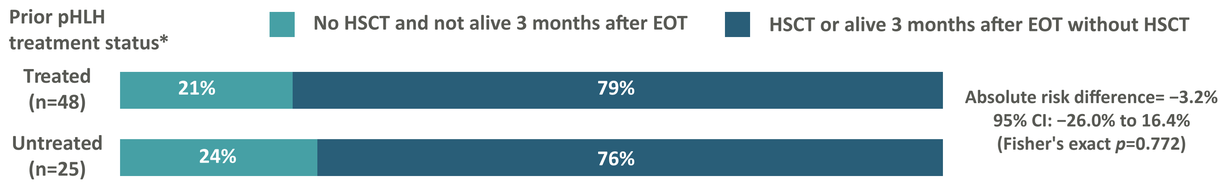
Figure 6: Prior pHLH treatment status did not affect the time to first investigator-assessed overall responses



CR, complete response; HLH, hemophagocytic lymphohistiocytosis; OR, overall response; PR, partial response.

- Rates of survival HSCT or ≥3-month post-EOT in previously treated (79%) and untreated patients (76%) patients were comparable underscoring emapalumab's potential utility irrespective of the line of therapy **(Figure 7)**.

Figure 7: Comparable survival to HSCT/alive ≥3 months post-EOT with emapalumab, regardless of prior pHLH therapy



*5 patients received <3 doses of emapalumab, 2 were protocol violations.
CI, confidence interval; EOT, end of treatment; pHLH, primary hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem-cell transplantation.

References: 1. Hatterer E, et al. *Cytokine*. 2012;59:570. 2. GAMIFANT™ (emapalumab-lzsg) injection, for intravenous use initial U.S. Approval: 2018; 3. Locatelli F, et al. *N Engl J Med.* 2020;382(19):1811-1822; 4. Jordan MB, et al. *Blood*. 2023;142(Supplement 1):1174; 5. Locatelli F, et al. EHA 2025. Milan, Italy.

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