Poster MDS-600

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Effects of Ianalumab Treatment on B-Cell Activation, Maturation, and Maintenance of Vaccine Titers in Patients With Primary Immune Thrombocytopenia (ITP) in the Phase 2 VAYHIT3 Study

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Key Findings and Conclusions

- A short course of ianalumab resulted in a rapid, profound, and sustained depletion of all B-cell subsets in peripheral blood, consistent with ADCC
- The increase in sBAFF indicates potent BAFF receptor blockade, while the decrease in sBCMA suggests reduced plasmablast burden and diminished B-cell differentiation and maturation
- Together, these findings support the novel dual mechanism of action of ianalumab, which results in enhanced B-cell depletion and inhibition of B-cell activation and survival, while preserving T- and NK cell populations as well as pre-existing vaccine-specific immune responses

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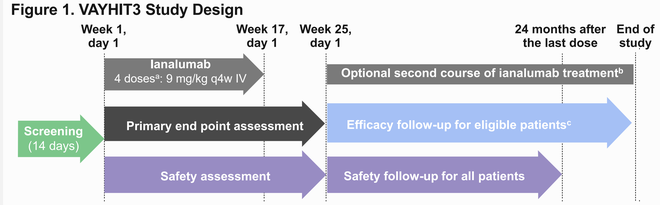
Introduction

- Ianalumab is a monoclonal antibody targeting B cells via a novel dual mechanism of action of enhanced B-cell depletion via antibody-dependent cellular cytotoxicity (ADCC) and inhibition of B-cell activation and survival via B-cell activating factor (BAFF) receptor blockade[1-3]
- In the phase 2 VAYHIT3 (NCT05885555) trial, a short course of ianalumab elicited potent and sustained clinical responses in heavily pretreated patients with immune thrombocytopenia (ITP)[4]
- The aim of this analysis was to examine the impact of ianalumab on B-cell counts, selected biomarkers of B-cell activation and regulation, and maintenance of pre-existing vaccine-specific antibody status

Methods

- VAYHIT3 was an open-label, single-arm study evaluating 4 once-monthly infusions of 9 mg/kg ianalumab in heavily pretreated patients with primary ITP. Concomitant treatment, including eltrombopag, was allowed **(Figure 1)**
- B-cell counts in peripheral blood were measured as a secondary end point. Exploratory end points included baseline and change from baseline measures in:
  - Soluble B-cell maturation antigen (sBCMA; marker of plasmablast maturation to plasma cells to assess B-cell differentiation and plasmablast burden)
  - Soluble BAFF (sBAFF; to confirm the inverse correlation between BAFF levels and B-cell counts)
  - T-, B-, and natural killer (NK) cell subsets
  - Antibody status from prior tetanus and measles vaccinations

Figure 1. VAYHIT3 Study Design



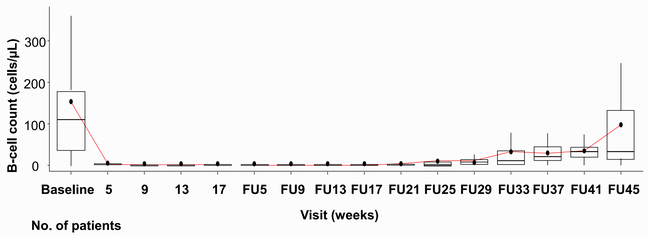
IV, intravenous; q4w, every 4 weeks.
[a]Patients received premedication prior to the first 2 ianalumab infusions (paracetamol 1000 mg, antihistamine as per institutional guidelines, and corticosteroids [prednisolone 50 mg or equivalent]). [b]Patients who had a confirmed response to the first course of ianalumab and who lost response after the week 25 visit were offered an optional second course of ianalumab treatment upon the investigator's decision. [c]Platelet count of ≥30 × 10^9/L without rescue or new ITP treatment.

Results

B-Cell Depletion

- In the full analysis set (N = 41), a short course of ianalumab resulted in a rapid, profound, and durable depletion of B cells, observed from the first postbaseline measurement onwards **(Figure 2)**
  - The median change from baseline was −98% at week 5 (before the second infusion) and −100% at week 13 (before the fourth infusion)

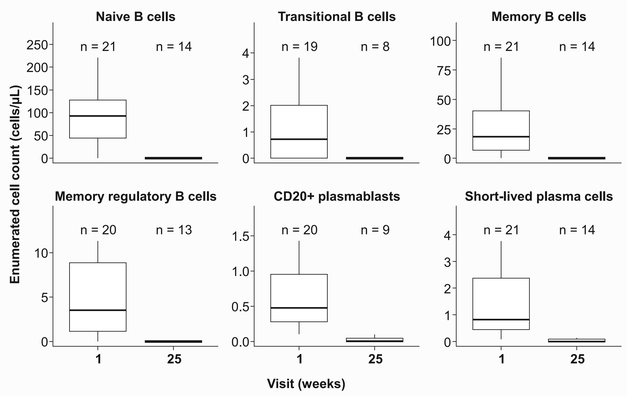
Figure 2. B-Cell Count Over Time



FU; follow-up
The boxes indicate the 25th and 75th percentiles; the horizontal line indicates the median. The dots in the boxes indicate the mean values. The whiskers extend to the minimum and maximum, or 1.5 × interquartile range outside the box if the minimum and maximum exceed that range. The number of patients at each timepoint reflects those with available B-cell count assessments; approximately 50% of baseline samples were not collected or had cancelled tests.

- Notably, depletion was observed across all measured circulating B-cell subsets, including naive, transitional, memory, and regulatory B cells, plasmablasts, and plasma cells **(Figure 3)**

Figure 3. Change in B-Cell Subsets



B-Cell Recovery

- Minimal B-cell recovery, defined as ≥80% of baseline and ≥14.8 cells/µL, or ≥50 cells/µL, was observed during the first 7 months from the last ianalumab infusion
- B cells started to recover approximately 7-8 months after the last infusion, with median (95% CI) time from last infusion to B-cell recovery being 12.2 (10.15-15.24) months **(Figure 4)**

Biomarker Levels

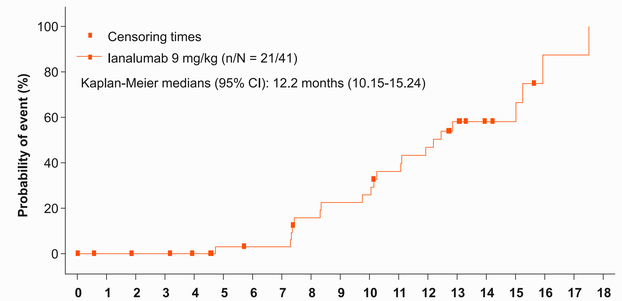
- In patients with baseline biomarker measurements, sBCMA concentrations decreased from treatment initiation to end of treatment that extended to week 25 and sBAFF levels increased from baseline after first ianalumab infusion **(Figure 5; Table 1)**
- There was no depletion of either CD4+ or CD8+ T cells, and NK-cell populations generally remained stable **(Figure 5; Table 1)**

Table 1. Percentage Changes from Baseline in Biomarkers

Biomarkers	EOT	Week 25
sBCMA, n	31	30
Median (IQR)	−48.3 (−55.1 to −33.0)	−44.0 (−56.8 to −35.0)
sBAFF, n	28	29
Median (IQR)	144.3 (74.3-351.8)	138.4 (39.2-273.0)
CD3+CD4+ T cells, n	16	18
Median (IQR)	2.3 (−3.8 to 15.3)	−6.4 (−14.5 to 40.7)
CD3+CD8+ T cells, n	16	18
Median (IQR)	4.1 (−6.1 to 22.1)	3.9 (−12.5 to 39.5)
NK cells, n	16	18
Median (IQR)	3.4 (−23.3 to 22.0)	3.9 (−35.3 to 24.2)

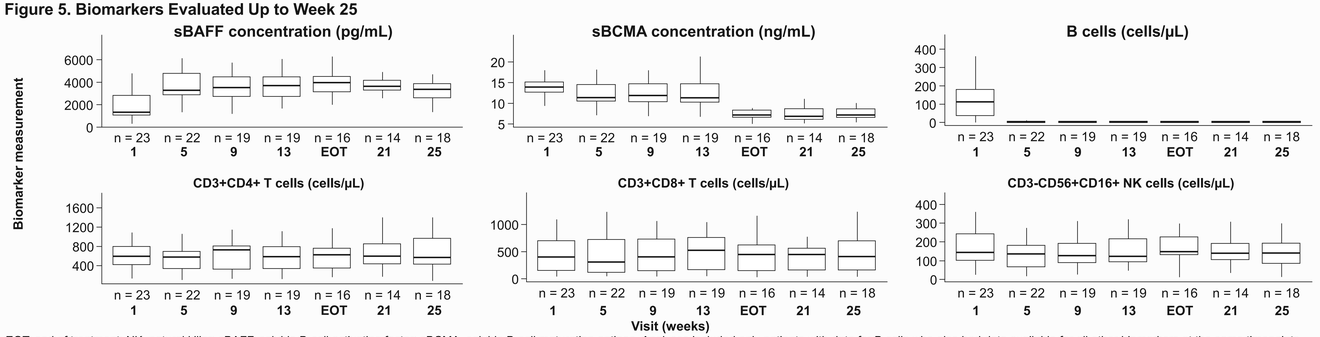
EOT, end of treatment; IQR, interquartile range; NK, natural killer; sBAFF, soluble B-cell activating factor; sBCMA, soluble B-cell maturation antigen. Sample sizes for each biomarker measurement included all patients with data available.

Figure 4. Kaplan-Meier Plot of Time From Last Ianalumab Infusion to B-Cell Recovery



B-cell recovery observed in 21 patients at the 1-year analysis data cut-off.

Figure 5. Biomarkers Evaluated Up to Week 25



EOT, end of treatment; NK, natural killer; sBAFF, soluble B-cell activating factor; sBCMA, soluble B-cell maturation antigen. Analyses included only patients with data for B cells who also had data available for all other biomarkers at the same timepoints.

Effect on Pre-Existing Humoral Immunity to Vaccination

- The effect of ianalumab on prior measles and tetanus immunization was evaluated at baseline, week 25, and 1-year after the final ianalumab infusion
- Overall, 30 patients had paired baseline and week 25 samples with valid results; all 30 patients had protective titers against measles (≥16.5 arbitrary units/mL) and protective titers against tetanus (≥0.10 international units/mL) at baseline
- At week 25, 29/30 patients maintained protective titers against measles and 29/30 maintained protective titers against tetanus
  - Details on prior vaccination in the 2 patients (1 each for measles and tetanus) who lost positive or protective status was unavailable; both had received intravenous immunoglobulin prior to baseline
- At the 1-year timepoint, all ten evaluable patients maintained protective titers against measles and tetanus

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