Poster# **PS2237**

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Ianalumab's Dual Mechanism of Action: Targeting B Cells Through Enhanced B-Cell Depletion and Blockade of B Cell-Activating Factor Receptor Signaling

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KEY FINDINGS & CONCLUSIONS

- Ianalumab, through its dual mechanism of action, addresses limitations of first-generation B-cell–targeting therapies for autoimmune and hematologic diseases by providing more potent B-cell depletion and additional BAFF-R blockade on remaining B cells.
- *In vivo*, ianalumab depletes B cells in the blood and lymphoid organs of healthy mice and leads to reduced disease activity in a murine ITP model.
- Accordingly, patients with ITP (NCT05885555) treated with ianalumab showed a reduction in disease activity in a phase 2 trial.[6] See Oral presentation #S312 on June 15, 2025.
- Ongoing phase 3 studies in first-line (1L) and second-line (2L) primary ITP (NCT05653349 and NCT05653219, respectively), wAIHA (NCT05648968), and additional autoimmune indications will provide further evidence on the efficacy and safety of ianalumab in larger patient populations.

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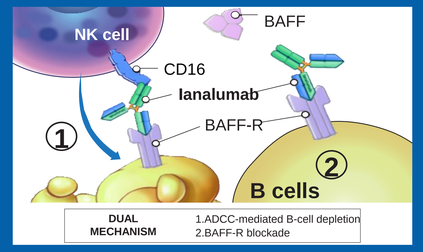
INTRODUCTION

- B cells are key drivers of disease activity in immune thrombocytopenia (ITP), warm autoimmune hemolytic anemia (wAIHA), and other systemic hematologic and auto-immune diseases, supporting B-cell depletion as an attractive therapeutic strategy in these patients.[1]
- However, survival signals mediated by high level of B cell-activating factor (BAFF) may interfere with B-cell depletion.[2]
- Ianalumab, a fully human afucosylated monoclonal antibody targeting BAFF-receptor (BAFF-R), has been shown to deplete B cells through enhanced antibody-dependent cellular cytotoxicity (ADCC) with concurrent blockade of BAFF:BAFF-R–mediated signals (**Figure 1**).[3]

Figure 1. Ianalumab's dual mechanism of action



ADCC, antibody-dependent cellular cytotoxicity; BAFF, B cell-activating factor; BAFF-R, BAFF receptor; CD16; cluster of differentiation 16; NK cell, natural killer cell.

OBJECTIVE

- To characterize the impact of ianalumab on various B-cell functions *in vitro*, as well as its ability to deplete circulating and tissue B cells in C57BL/6 (B6) mice and in an established active mouse model of ITP.[4]

METHODS

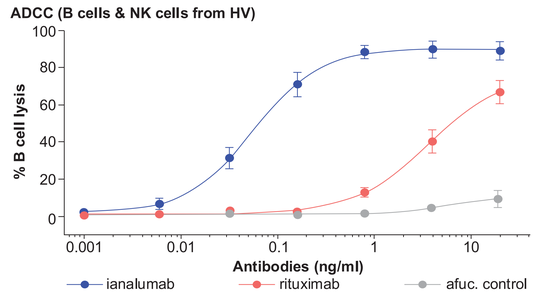
- *In vitro* B-cell killing was assessed using isolated NK cells and B cells from healthy volunteers (HV). Ri-1 B cells were also used as target cells.
- *In vitro* blockade of BAFF stimulation was evaluated through Western blots of BAFF-R and Nuclear Factor Kappa B Subunit 2 (NFkB2) intact and cleaved forms, and B-cell proliferation measured by ^{3}H-thymidine incorporation.
- The efficacy of B-cell depletion following administration of ianalumab in B6 mice and in an active mouse model of ITP was investigated using flow cytometry and ELISA.

RESULTS

In vitro B-cell killing

- In an ADCC assay co-culturing purified NK cells with B cells from HV, ianalumab showed a ~60-fold increased potency compared to rituximab (**Figure 2**). This increased potency was also observed when Ri-1 target.

Figure 2. Ianalumab shows superior potency to rituximab in ADCC



Primary B cells and NK cells from HV (N=6 donors) were co-cultured in the presence of ianalumab, rituximab or an irrelevant afucosylated antibody, and B-cell lysis was evaluated after 4h.
ADCC, antibody-dependent cellular cytotoxicity; HV, healthy volunteers; NK, natural killer; SLE, systemic lupus erythematosus.

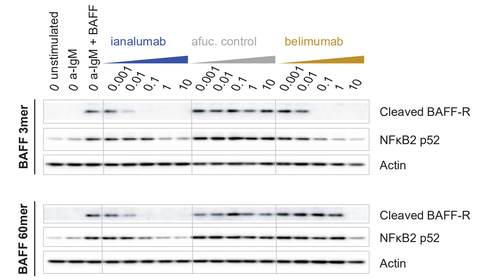
In vitro blockade of BAFF stimulation

- Ianalumab effectively prevented BAFF from binding to BAFF-R–expressing cells (data not shown). This blockade of BAFF-R on human B cells correlated with the effective inhibition of BAFF-induced cleavage of BAFF-R and NF-κB2 (**Figure 3**).
- The inhibition of BAFF-R signaling by ianalumab led to the inhibition of BAFF-R–dependent B-cell functions, like B-cell proliferation (**Figure 4**) and IgG production (not shown).
- Notably, ianalumab was able to inhibit B-cell signaling and proliferation with the same potency, when induced by a BAFF trimer or 60mer in contrast to belimumab which had less potent inhibitory effects on the BAFF 60mer (**Figures 3 & 4**).

In vivo B-cell depletion

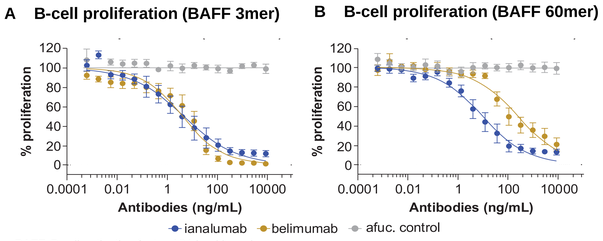
- *In vivo,* ianalumab induced a significant reduction of most B-cell subpopulations in the blood and lymphoid organs of B6 mice. In the spleen, the level of depletion at 4 days after a single dose of ianalumab correlated with the surface expression of BAFF-R, as well as the ability of the cells to recirculate (**Figure 5A**). Longer exposure to ianalumab led to a decrease of tissue resident cells like marginal zone (MZ) B cells (**Figure 5B**).[5]
- Ianalumab treatment also led to a decrease of CD21/CD35 expression on the B cells that were not depleted, suggesting a blockade of BAFF-R signaling on these cells (**Figure 5C**).[5]

Figure 3. Ianalumab inhibits the cleavage of BAFF-R and NFkB2 induced by BAFF



Primary B cells from HV were stimulated for 24 h with a combination of BAFF 3mer or 60mer (50 ng/mL) and anti-IgM (0.5 mg/mL) in the presence of ianalumab, belimumab, or an irrelevant afucosylated antibody. The presence of cleaved BAFF-R and cleaved NFkB2 was analyzed after 24 h by Western blot.
BAFF, B cell-activating factor; NFkB2, Nuclear Factor Kappa B Subunit 2; R, receptor.

Figure 4. Ianalumab inhibits proliferation of human B cells

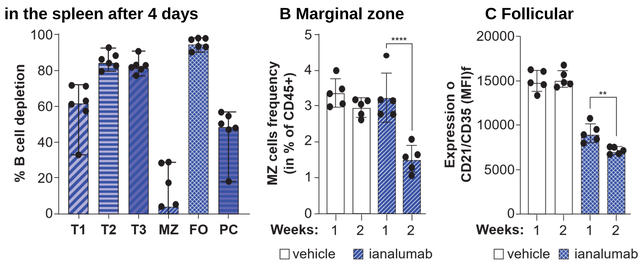


BAFF, B cell-activating factor; HV, healthy volunteers.
Primary human B cells from HV (N=10 donors) were co-stimulated by BAFF 3mer (**A**) or BAFF 60mer (**B**) and anti-IgM. Cell proliferation was measured by 3H-thymidine incorporation after 72 h.

In vivo efficacy in an active mouse model of ITP

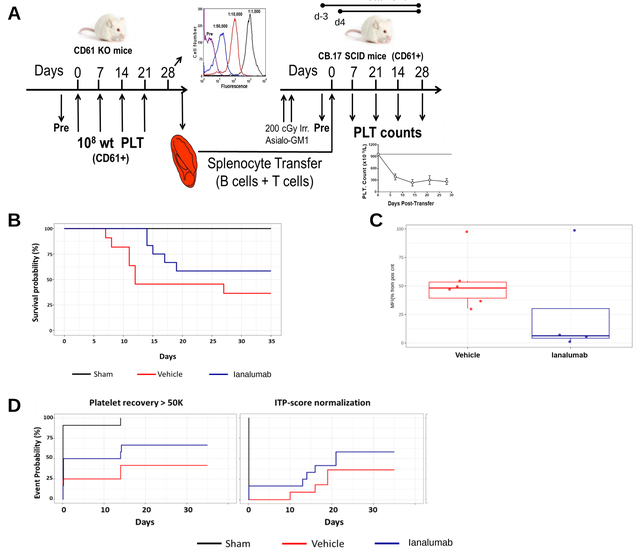
- In addition, severe combined immunodeficiency (SCID) mice with ITP treated with ianalumab (**Figure 6A**) had significantly reduced blood B-cell counts, and a trend toward reduced ITP-related mortality (**Figure 6B**). Additionally, ianalumab treatment resulted in a reduction in anti-platelet antibody levels compared with the ITP control group at the peak of ITP-related mortality 2-3 weeks post disease induction (**Figure 6C**). Compared with the ITP control, ianalumab treatment resulted in higher platelet counts with an earlier time to recovery (platelet counts >50k/μL) and improved scores of disease severity (**Figure 6D**).

Figure 5. Ianalumab reduces most B-cell populations in spleen of B6 mice



B6 mice treated with single treatment 10 mg/kg (**A**) or twice weekly 100 mg/kg intraperitoneally (i.p.) (**B, C**) ianalumab. Percentage of B-cell depletion 4 days post-treatment (**A**), frequency of MZ cells (**B**) and expression of CD21/CD35 (**C**) in the spleen after 1 or 2 weeks of treatment. Quantification via flow cytometry: CD23$^+$ CD21/35$^{-/low}$ IgM^{high} IgD^{high}; T3 (transitional 3): CD23$^+$ CD21/35$^{-/low}$ IgM^{low} IgD^{high}; MZ (marginal zone): CD23$^+$ CD21/35^{high} IgM^{high} IgD^{low}; FO (follicular): CD23$^+$ CD21/35^{int} IgD^{high}; PC (plasma cells): CD138$^+$CD267$^+$.

Figure 6. Ianalumab has beneficial effects in an active mouse model of ITP



(**A**) SCID mice induced to develop ITP were treated with ianalumab at a dose of 100 mg/kg, administered i.p. weekly over 5 weeks. Treatment started either 3 days prior to disease induction or 4 days after. Results from two separate studies were pooled and analyzed. Survival curves (**B**), anti-platelet antibody levels (**C**), time to platelet recovery >50k/mL and time to normalization of ITP scores (**D**) are shown. For statistical analysis, the log-rank test was used for survival and time-to-event curves; unpaired t test, ANOVA and Tukey`s HSD tests were used for box plot.
CD, cluster of differentiation; KO, knock-out, PLT, platelets; SCID, severe combined immunodeficiency; wt, wild-type.

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Disclosures

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