

Zanubrutinib for the Treatment of Cold Agglutinin Disease: Primary Analysis of the Phase II Hovon169 Study

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Background

Cold agglutinin disease (CAD) is a rare autoimmune hemolytic anemia, typically associated with a B cell clone in the bone marrow (BM) and an IgM kappa paraproteinemia. While similar to Waldenstrom Macroglobulinemia (WM), the CAD clone is typically MYD88 wild-type. The CA's are IgM anti-erythrocyte auto-antibodies leading to complement-mediated hemolysis and agglutination-mediated cold-induced peripheral symptoms (CIPS). An unmet need exists for well-tolerated and effective treatments targeting both hemolysis and CIPS. Zanubrutinib, a second-generation covalent Bruton's tyrosine kinase (BTK) inhibitor, shows high efficacy and tolerability in similar B cell non-Hodgkin lymphomas including MYD88 wild-type WM. Given the pathophysiologic overlap between CAD and WM, and promising retrospective data on ibrutinib in CAD, we hypothesized that zanubrutinib would be an effective and safe therapeutic option.

Aim

To investigate the efficacy and safety of zanubrutinib in CAD.

Methods

HOVON169 is a phase IIb, non-randomized, multinational trial (NCT06067048), including CAD patients relapsed/refractory after ≥ 1 prior therapy or non-eligible for other CAD therapy, with a treatment-indication (Hb ≤ 10 g/dL and/or grade 2 CIPS). Patients were treated with zanubrutinib 320mg daily, in 4-weeks cycles. Primary endpoint evaluation after cycle 6 used CAD overall response rate (ORR) as composite endpoint (Figure). Secondary endpoints included IgM response, CIPS response, transfusion dependence, and CTCAEv5.0-graded toxicities.

Results

Of 25 included patients, 12 (48%) were female. Median age was 73 years (range 56-82). Most patients (22; 88%) were previously treated, with a median of 2 lines (range 1-8). Prior treatment included rituximab monotherapy (19; 76%), immunochemotherapy (7; 28%), corticosteroids (6; 24%), and complement inhibitors (4; 16%). Twenty-three (92%) had an M-protein, and 17 (68%) clonal CD20+ BM disease. At central BM revision of 24 evaluable cases using WHO-HAEM5, 12 (50%) were classified as CAD-associated lymphoproliferative disorder, 4 (17%) as unclassifiable clonal disease, 1 (4%) as plasma cell dyscrasia, no clonal disorder was detectable in 7 (29%). Treatment indications were Hb ≤ 10.5 g/dL (n=7), grade 2 CIPS (n=8), or both (n=10). At start, 9 patients were transfusion-dependent. 20 out of 25 patients completed the first 6 cycles. CAD ORR was 6/25 (24%), all partial responses (Figure). Five patients discontinued treatment prematurely due to lack of response/patients' decision (n=3), progressive IgM (n=1), or death (n=1). Transfusion-dependence resolved in 6/9 patients (67%), while 2 patients developed transfusion-dependence during zanubrutinib treatment. Of 18 patients with grade 2 CIPS at baseline, 8 (44%) experienced improvement, of whom 4 complete resolution. IgM ORR was 4 (16%), while 16 (64%) had stable disease, one progression (4%), and 4 (16%) were unevaluable. A total of 17 (possibly) treatment-related AEs grade ≥ 2 occurred in 10 patients, most commonly grade 2 gastrointestinal symptoms. Five were grade 3 AEs (pneumonia, constipation, hypertension, anemia, and atrial fibrillation). There was 1 death due to non-neutropenic sepsis and heart failure in the context of pre-existing heart disease.

Summary/Conclusion

Our study did not meet its primary endpoint, with a CAD ORR of only 24%. This unexpected limited efficacy reinforces classification of CAD as a distinct entity, and underscores the need for specific trials in this condition.

Figure. CAD response criteria and response rates after 6 cycles of zanubrutinib treatment

	Hemolytic anemia 	CIPS* 	Transfusion dependence** 	IgM response*** 	Patients meeting response criteria N=25
Complete CAD response	Hb > LLN Haptoglobin > LLN	& No CIPS	& Transfusion independence	& No IgM progression	None
Partial CAD response	Δ Hb $\geq$ 1.5 g/dL or > LLN	& $\geq$ 1 grade improvement	& Transfusion independence	& No IgM progression	6 (24%)
No CAD response	No PR or CR				19 (76%) <i>Of whom 5 premature discontinuation</i>

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*CIPS grading; Grade 0: no such symptoms; Grade 1: acrocyanosis/Raynaud-like peripheral symptoms, not interfering with daily living; Grade 2: acrocyanosis/Raynaud-like peripheral symptoms, interfering with daily living; Grade 3: gangrene or ulcerations

**Transfusion dependence at baseline was defined as ≥ 1 RBC transfusion in prior 6 months or ≥ 2 RBC transfusions in prior 12 months. Transfusion independence at primary endpoint was defined as no RBC transfusion from cycle 3 to 6.

***IgM response was classified according to the 11th International Workshop on Waldenström's Macroglobulinemia criteria, progression being $\geq 25\%$ increase in serum IgM level with minimum increase of 5 g/L from lowest nadir

Abbreviations: CAD = cold agglutinin disease; CIPS = cold-induced peripheral symptoms; CR = complete response; Hb = hemoglobin; LLN = lower limit of normal; PD = progressive disease; PR = partial response; RBC = red blood cell

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Special Instructions: Anne-Marie Becking is the first author but will not be able to attend the meeting.

Thus, Dr. Josephine Vos would be the presenting author for this abstract.

The abstract has been presented previously at EHA 2026 (Stockholm)

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