

HOVON 169: Phase II trial of Zanubrutinib in Cold Agglutinin Disease

Anne-Marie L. Becking¹, Marie José Kersten^{1,2} & Josephine M.I. Vos^{1,2}

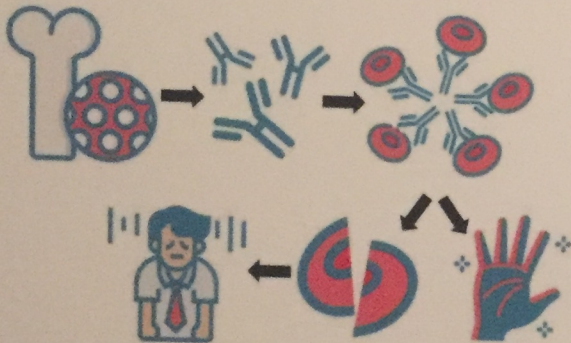
On behalf of the writing committee: S. Berentsen, M.C. Minnema, S. D'Sa, D. Evers, L.E.M. Oosten, G.E. Tjønnfjord, M. de Haas, B. Tore Gjertsen & L. Koens

Background

Cold Agglutinin Disease (CAD) is a rare form of auto-immune hemolytic anemia, caused by IgM secreting lymphomas such as Waldenström macroglobulinemia (WM), IgM MGUS or CAD-LPD.

In CAD, IgM antibodies react at low temperatures and cause agglutination and destruction of red blood cells (hemolysis).

This results in anemia and cold-induced symptoms (CIPS), such as pain and discoloration in acral areas.



Treatment of CAD includes supportive care ("keep warm"). Some patients require therapy that is directed at the malignant cells:

- Rituximab: efficient in some patients (±50%), but with short effect duration (<1 year).
- Chemotherapy: higher efficacy, but accompanied by more side effects.
- Sutimlimab: shows promising results on hemolytic anemia, but do not improve CIPS.

Zanubrutinib, a selective Bruton's tyrosine kinase inhibitor (BTKi), is shown to be effective in WM, in patients with and without MYD88 mutation (ASPEN trial). Due to similarities between CAD and WM, we hypothesize that zanubrutinib could also be effective in CAD.

Retrospective data have already shown that ibrutinib, a similar but less selective BTKi, can be effective for CAD.

Aim

To evaluate the effect of zanubrutinib treatment in patients with CAD, on hemolytic anemia as well as CIPS

Method

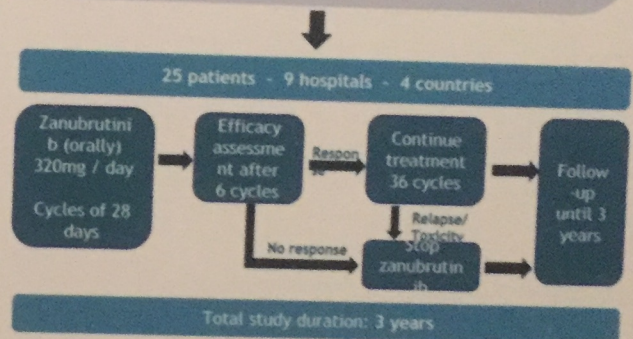
Investigator initiated phase II trial, trial management by HOVON, funding by BeiGene.

Key inclusion criteria

- Active CAD
- Clonal B-cell lymphoproliferative disorder: M-protein or malignant B-cell lymphoproliferation in bone marrow
- Treatment indication: Hb ≤ 10.5 g/dL or considerable CIPS

Key exclusion criteria

- Secondary CA to infections, rheumatological disorders, or chronic lymphocytic leukemia
- Extramedullary (outside the bone marrow) disease
- Previous treatment with BTK inhibitors



Outcome measurements

- ❖ CAD response after 6 cycles, based on:
 - Signs of anemia or hemolysis
 - CIPS
 - Transfusion dependence
 - Hematological progression
- ❖ Time to response & time to best response
- ❖ Progression free survival & overall survival
- ❖ Hematological response, based on IgM levels
- ❖ Safety and tolerability
- ❖ Effect on patient-reported outcomes:
 - Fatigue
 - Quality of life
 - CIPS