Study ID: bioMAZINGA

Title of the study: Non-invasive monitoring of *MYD88*^{L265P} in patients with anti-MAG antibody neuropathy treated with zanubrutinib (bioMAZINGA).

The MAZINGA trial sponsored by Padova University Hospital in collaboration with the University of Turin and supported the BeiOne Medicine (formerly known as BeiGene, the company that will provide the drug free of charge), is a multicenter, open label, single arm phase II trial to evaluate the activity, safety and tolerability of zanubrutinib in patients with symptomatic IgM related anti-MAG antibody neuropathy (aMAG-NP).

The primary endpoint of the bioMAZINGA study is the decrease of MYD88L265P plasma cell-free DNA (cfDNA) burden, as assessed by cfDNA, after 12 months of zanubrutinib.

Among the secondary endpoints of the bioMAZINGA study, there is also the kinetic of mutation after treatment with zanubrutinib, the correlation of decrease MYD88L265P burden in the cfNDA with neurological response, hematological response, ENG/EMG parameters and Quality of life (QoL) readouts.

Update of the MAZINGA trial.

Due to bureaucratic delays on the part of the ethics committee (EU CT number: 2025–523091–23-00), approval for the study was delayed, but we (as Padova center) have already managed to recruit a few patients.

Three centers have already been activated and another five will be activated in the next three months, allowing us to reach the target number of patients (30 in total) in the next seven months, ahead of schedule.

In Figure 1 a recruitment chart shows that, despite the delay in starting the study, we have returned to the recruitment program.

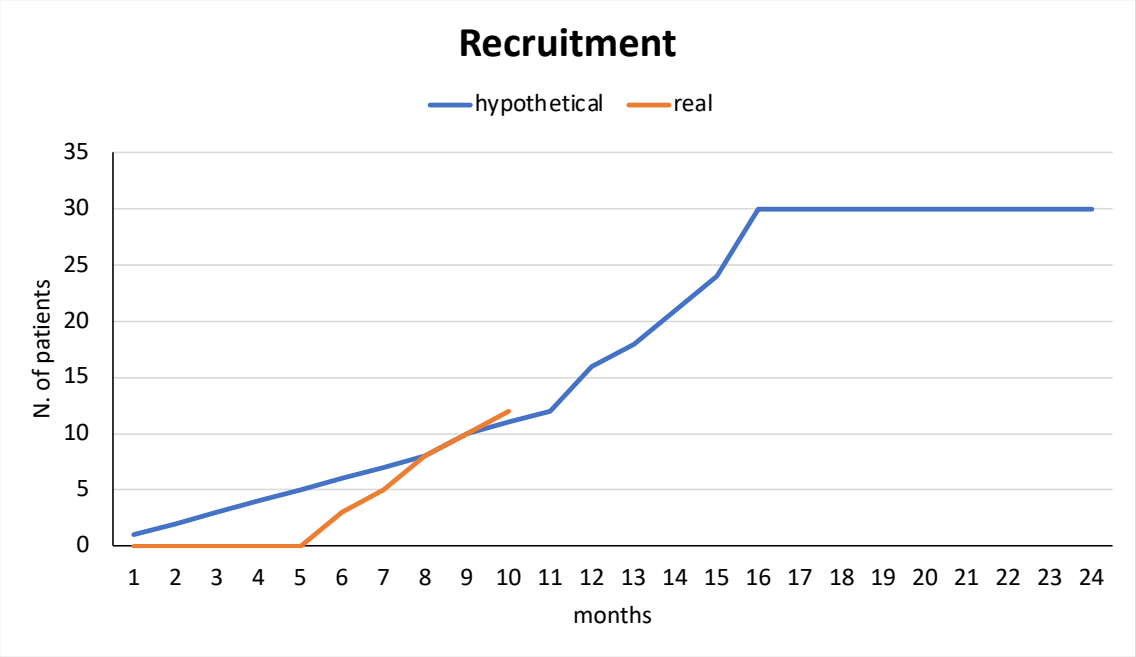

Figure 1. Recruitment plan of BioMAZINGA.

Primary endpoint of the MAZINGA trial is the proportion of patients with neurological improvement defined as improvement of at least 1 point in at least 2 neurological scales (ONLS, INCAT disability, INCAT sensory sum scores (ISS), MRC sum score, I-RODS functional score) at 12 months of zanubrutinib treatment.

Secondary endpoints are:

● the proportion of patients with neurological improvement after 24 and 48 months of zanubrutinib;

● the proportion of patients with ENG/EMG improvement since the baseline, assessing decrease of distal motor latency, increase of terminal latency index, increase of sensory nerve action potential amplitude (see criteria of evaluation) at upper limbs after zanubrutinib treatment at 12, 24 and 48 months;

● levels of monoclonal protein, IgM and of anti-MAG antibody titers at 12, 24 and 48 months.

● Type, frequency and severity of adverse events, severe adverse event and adverse event of special interest with zanubrutinib in patients with anti–MAG antibody neuropathy;

● Overall response rate, defined as the proportion of patients achieving complete response (CR), very good partial response (VGPR), partial response according to guidelines;

● Event free survival, defined as time from the start of therapy to relapse or death or start of a new therapy (event) or last known follow-up (censured);

● Time to progression, defined as time from the start of therapy to the worse of neurological symptoms defined as worse of at least 1 point in at least 2 neurological scales such as Overall Neuropathy Limitations Scale (ONLS), INCAT disability, INCAT sensory sum scores (ISS), MRC sum score, I-RODS functional score after the nadir

● overall survival, defined as time from the start of therapy to death (event) or last known follow- up (censured).

Preliminary results of the bioMAZINGA study.

To date, 12 patients with aMAG-NP have already been recruited (all from the Hospital University of Padova).

The media age was starting treatment was 69 years (IQR 57-81 years), all had Waldenstrom macroglobulinemia and IgM/K paraprotein, the average levels of paraprotein was 6.6±2.3 g/L, creatinine levels 78±23 μmol/L, free-light chain K 259±68 mg/L, free-light chain lambda 20±12 mg/L, LDH 213 U/L.

The duration of treatment is shown in Figure 1, mean 4.2±2.0 months.

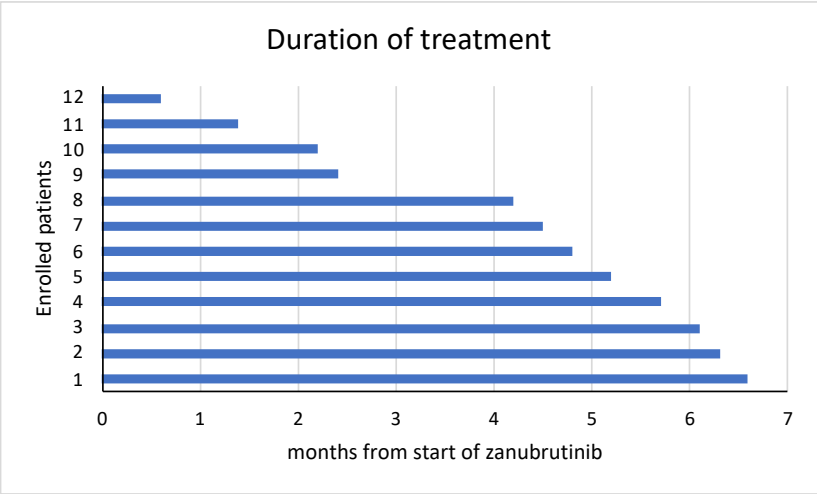

Figure 1. Swimmer plot of duration of treatment with zanubrutinib.

All patients harbored MYD88 L265P mutation in bone marrow by Allele specific PCR (AS-PCR). Upon preliminary assessment of baseline cfDNA, 10 of 12 of these patients had the MYD88 L265P mutation in their cfDNA. The concordance rate was 83.3% (Figure 2).

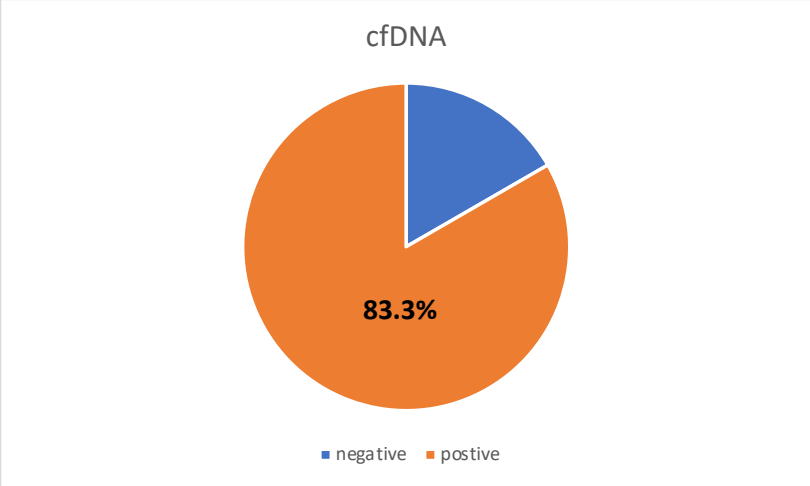

Figure 2. Pie chart of concordance between MYD88 L265P assessed by plasma cfDNA and allele specific PCR (AS-PCR) assessed in the bone marrow.

This supports the hypothesis that cfDNA may be a noninvasive surrogate marker for MYD88 L265P detection in patients with aMAG-NP.

To fulfill the secondary endpoint of the kinetic of mutation, we are collecting the samples for cfDNA analysis at different time points after starting zanubrutinib therapy (the samples will be centralized for analysis every 6 months).