

Trial in Progress. Zanubrutinib, a Second Generation BTK Inhibitor, in Anti-MAG Antibody Neuropathy: a Phase II Italian Multicenter Clinical Trial (MAZINGA).

Andrea Visentin¹, Alessandro Cellini¹, Francesco Angotzi¹, Nicolò Danesin¹, Alessandro Salvalaggio², Benedetta Tierro², Giacomo Maria Minicuci², Eros Cerantola², Anna Maria Frustaci³, Francesco Zaja⁴, Simone Ferrero⁵, Bruni Ferrero⁶, Francesco Autore⁷, Luca Laurenti⁷, Girolama Alessandra Marfia⁸, Pietro Doneddu⁹, Marzia Varettoni¹⁰, Angelo Schenone¹¹, Francesco Piazza¹, Livio Trentin¹, Chiara Briani²

1 Hematology unit, Department of Medicine, University of Padova, Azienda Ospedale Università Padova, Padova, Italy;

2 Neurology Clinic, Department of Neuroscience, University of Padova, Azienda Ospedale Università Padova, Padova, Italy;

3 Department of Hematology, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy;

4 DSM, University of Trieste and UCO Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste, Italy;

5 Department of Molecular Biotechnology and Health Sciences, University of Torino and Division of Hematology, AOU Città della Salute e della Scienza di Torino, Torino, Italy;

6 Division of Neurology, AOU Città della Salute e della Scienza di Torino, Torino, Italy

7 CLL Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy;

8 Department of Systems Medicine, Immunomediated Neuropathies Unit, Tor Vergata University Hospital, Roma, Italy;

9 Neurology Unit, Humanitas University, Rozzano – Milano, Italy;

10 SC Ematologia 1, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;

11 Neurology Clinic, University of Genova, San Martino Hospital, Genova, Italy.

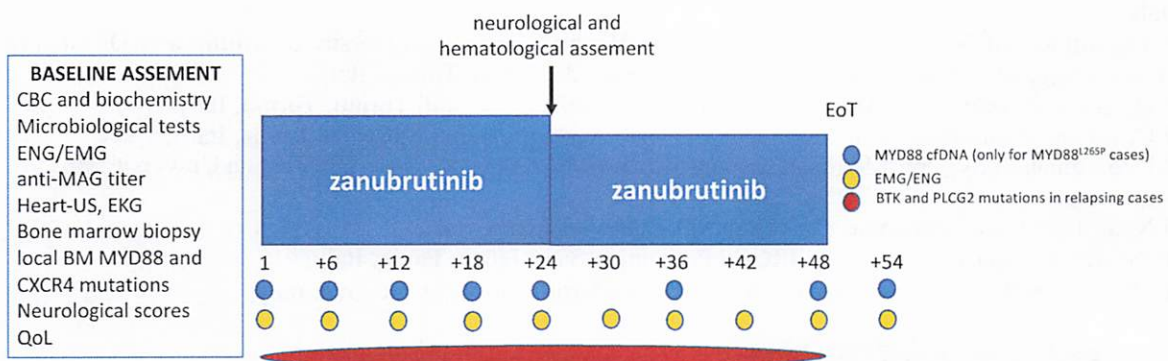
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Introduction. Anti-myelin-associated glycoprotein (anti-MAG) antibody neuropathy is the most common monoclonal gammopathy of neurological significance (MGNS), associated with IgM monoclonal gammopathy of undetermined significance (MGUS), Waldenström macroglobulinemia (WM), or other indolent B-cell malignancies. Patients typically experience progressive sensory loss, gait impairment, tremor, weakness and disability. Current therapeutic options, including rituximab-based approaches, produce heterogeneous responses and often fail to achieve sustained neurological improvement. Almost 60% of patients with anti-MAG neuropathy harbor MYD88 L265P mutation supporting the Bruton's tyrosine kinase (BTK) pathway downstream to the BCR and TLR signaling cascades. Thus, BTK inhibitors have emerged as promising targeted therapies through suppression of pathogenic B-cell signaling and IgM production. The MAZINGA trial (NCT07392229) is a multicenter Italian phase II study designed to evaluate the efficacy and safety of zanubrutinib, a second-generation BTK inhibitor, in patients with anti-MAG neuropathy

Methods. MAZINGA (NCT07392229) is an investigator-initiated, multicenter, open-label, single-arm phase IIA clinical trial. Eligible patients must demonstrate anti-MAG demyelinating polyneuropathy, antibody titers ≥ 7.000 BTU, an underlying IgM monoclonal gammopathy (either IgM MGUS, WM, or other B-cell indolent lymphoma), EMG/ENG evidence of demyelination, and measurable neurological disability (ONLS at lower limbs at least ≥ 1 and/or INCAT ≥ 2). We excluded patients with aggressive lymphoma, ECOG >3 or INCAT at lower limbs ≥ 4 . Both treatment-naïve and relapsed/refractory patients are eligible. The primary endpoint is clinically meaningful neurological improvement after 12 months, defined as an improvement of at least one point in at least two validated neurological scales, including the Overall Neuropathy Limitations Scale (ONLS), INCAT Disability Score, INCAT Sensory Sum Score (ISS), Medical Research Council (MRC) sum score, and Inflammatory Rasch-Built Overall Disability Scale (I-RODS). Secondary endpoints include neurophysiological responses, hematologic response rates, event-free survival, time to neurological progression, overall survival, and treatment-related safety outcomes, quality of life assessment and kinetics of cell-free DNA. Participants will receive oral zanubrutinib 160 mg BID for 24 months; those showing at least a stabilization of the neuropathy will proceed up to month 48 (Figure 1). Considering a one-sided z test for one-sample proportion, a level of significance of 5%, a power of the study equal to 80%, and assuming that the proportion of patients with improvement of 50%, the number of patients needed to be studied is 45.

Hypothesizing a study withdrawal of up to 10%, we plan to screen 50 patients. As per 30Jul2026 the trial is opened in 5/9 sites and enrolled 33% of the patients

Conclusion. The MAZINGA trial represents a novel and highly multidisciplinary approach to anti-MAG neuropathy, integrating expertise from hematology, neurology and neurophysiology. Our trial complements ongoing studies such as the ACALA-R trial (NCT05065554), which combines the BTK inhibitor acalabrutinib with rituximab, and the MAGNAZ trial (NCT07392229) which investigate zanubrutinib plus rituximab. The results of MAZINGA are expected to provide prospective evidence regarding the efficacy, safety, and neurological impact of zanubrutinib and may establish a new treatment paradigm for this rare disabling disorder and hopefully to refine the treatment landscape of anti-MAG neuropathy. The study is currently active and recruiting participants across 9 Italian centers



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Last Name: VISENTIN

Email: andrea.visentin@unipd.it

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