AOU Città della Salute e della Scienza di Torino – PO Molinette

Protocolli di Ricerca Clinica in ambito oncologico:

Disordini linfoproliferativi AOU CDSS

Divisione Universitaria di Ematologia (Prof. Benedetto Bruno)

Divisione Ospedaliera di Ematologia (Dott. Freilone Roberto)

Titolo:	MAZINGA. "ZANUBRUTINIB, A SECOND GENERATION BTK INHIBITOR, IN ANTI-MAG ANTIBODY NEUROPATHY: A PHASE II ITALIAN MULTICENTER CLINICAL TRIAL"
Patologia:	Neuropatia da anticorpi anti MAG (malattia di Waldenstrom, MGUS IgM)
Tipo di Studio:	INTERVENTISTICO, SINGOLO BRACCIO
Fase:	II
Principali criteri di inclusione:	• Age ≥18 years; • diagnosis of anti-MAG antibody polyneuropathy; • Neurophysiological (ENG/EMG) evidence of a demyelinating polyneuropathy with evidence of disproportionately prolonged distal motor latency in one or more nerves -excluding the median nerve if related to carpal tunnel syndrome- [Joint Task Force of the EFNS and the PNS, 2010]. • IgM monoclonal protein underlying MGUS (based on the WHO definition of clonal lympho- plasmocytes <10%), Waldenstrom macroglobulinemia (based on the WHO definition of clonal lympho-plasmocytes ≥10%), marginal zone lymphoma, chronic lymphocytic leukemia or low- grade lymphoma not otherwise specified; • Presence of anti MAG antibodies (titer □ 7.000 BTU); • Neurophysiological (ENG/EMG) evidence of demyelinating polyneuropathy; • ONLS at lower limbs at least ≥1 and/or INCAT ≥2. • Adequate bone marrow function as defined by: a. Absolute neutrophil count (ANC) ≥ 1000/mm3 b. Platelet ≥ 75,000/mm3 • Women of childbearing potential (WOCBP1) should avoid becoming pregnant while taking Brukinsa and for up to 1 month after ending treatment. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and source

	documented) or agree to use highly effective methods of contraception: • Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation - Oral, intravaginal, or transdermal • Progestogen-only hormonal contraception associated with the inhibition of ovulation - Oral, injectable, implantable • An intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomized partner • Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day before the first dose of study treatment, for the duration of the study, and for ≥ 90 days after the last dose of zanubrutinib, for ≥ 28 days after the last dose of lenalidomide, or according to the approved obinutuzumab and rituximab product/prescribing information, whichever is later). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post ovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception. Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and, if used, this method must be used in combination with another acceptable method listed above. For patients using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used. • Male patients with a female partner of childbearing potential are eligible if abstinent, vasectomized or if they agree to the use of barrier contraception with other methods or agree to use a condom during sexual contact with a pregnant women or a women of childbearing potential during the study treatment period and for ≥ 90 days after the last dose of zanubrutinib. 1 WOCBP is a woman who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Principali criteri di esclusione:	• Previous treatment with BTK inhibitors • Aggressive non-Hodgkin lymphoma or IgM multiple myeloma • Evidence of moderate or severe motor nerve axonal damage, defined when occurring diffuse polyneuropathic denervation or a recruitment pattern lower than intermediate in ≥50% of muscles examined, and/or INCAT at lower limbs ≥4. • ECOG >3 • Requiring ongoing therapy with strong or moderate cytochrome P450 3A (CYP3A) inducer. Use of strong/moderate CYP3A inducers within 14 days prior to the first dose of zanubrutinib (see Drug-interaction section). • creatinine clearance <30mL/min • Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase> 2.5 × upper limit of normal (ULN); Serum total bilirubin >2 x ULN. • presence of other possible causes of neuropathy, such as active HCV infections, diabetes- neuropathy, POEMS syndrome, CANOMAD syndrome, etc. • Any co-existing medical or psychological condition that would preclude participation in the study or compromise the ability to give informed consent. • History of severe bleeding disorder such as hemophilia A, hemophilia B, von Willebrand disease, or history of spontaneous bleeding requiring blood transfusion or other medical intervention. Requires ongoing treatment with warfarin or warfarin derivatives. History of stroke or intracranial hemorrhage within 6 months before first dose of study drug • Any uncontrolled or clinically significant cardiovascular disease including the following: a. Myocardial infarction within 6 months before screening b. Unstable angina within 3 months before screening c. New York Heart Association class III or IV congestive heart failure d. History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes) • Active fungal, bacterial and/or viral infection requiring systemic therapy • Known active infection with HIV, or serologic status reflecting active hepatitis B or C infection as follows: a. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with

	presence of HBcAb, but absence of HBsAg, are eligible if hepatitis B virus (HBV) DNA is undetectable (< 20 IU), and if they are willing to undergo monitoring every 4 weeks for HBV reactivation. b. Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible if HCV RNA is undetectable. • Pregnant or lactating women. • Vaccination or requirement for vaccination with a live vaccine within 28 days prior to the first dose of study drug or at any time during planned study treatment • Ongoing alcohol or drug addiction or any psychiatric condition(s) which would compromise ability to comply with study procedures. • Hypersensitivity to zanubrutinib or any of the other ingredients of the applicable study drugs. • Underlying medical conditions that, in the investigator's opinion, will render the administration of study treatment hazardous or obscure the interpretation of safety
Sede e contatti	TORINO, MOLINETTE Divisione Universitaria di Ematologia PI: Prof. Simone Ferrero (simone.ferrero@unito.it) Study Coordinator: Irene Scavini (irene.scavini@unito.it)