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:	go43878* "a phase iii, open-label, multicenter, randomized study evaluating glofitamab as a single agent versus investigator's choice in patients with relapsed/refractory mantle cell lymphoma"
Patologia:	Linfoma mantellare RECIDIVA
Tipo di Studio:	interventistico, randomizzato
Fase:	III
Principali criteri di inclusione:	• Age > 18 years at the time of signing Informed Consent Form • Life expectancy > 12 weeks Histologically-confirmed MCL, with documentation of either overexpression of cyclin D1 or the presence of t(11:14) • Relapsed or refractory disease, defined as follows: • – Relapse disease: defined as disease progression after the last regimen • – Refractory disease: defined as failure to achieve a PR or CR to the last • regimen • • At least one (1) line of prior systemic therapy • – Prior therapy must have included a BTK inhibitor and another systemic therapy • option (e.g., a regimen containing CD20 monoclonal antibody, prior • chemotherapy, targeted agent therapy such as bortezomib, etc.) • – Participants must have progressed or relapsed after completing BTK • inhibitor therapy, or failed to achieve a PR following 12 weeks of BTK • inhibitor therapy • – Participants intolerant to BTK inhibitor therapy who are unable to

	• complete at least 12 weeks of BTK inhibitor therapy should be excluded – Local therapies (e.g., radiotherapy) will not be considered as lines of therapy • • Confirmed availability of tumor tissue, unless deemed unsafe per investigator • assessment. Pretreatment collected biopsy is preferred. Recent archival tissue is • acceptable • • At least one bi-dimensionally measurable (defined as □ 1.5 cm) nodal lesion, or one • bi-dimensionally measurable (□ 1 cm) extranodal lesion, as measured on CT scan • • ECOG Performance Status of 0, 1, or 2 • • For participants enrolled in France: • - SARS-CoV-2 PCR testing and negative result within 48 hours before study • treatment administration at each treatment cycle • - Vaccination status in line with French National guidelines/recommendations • (COSV, ANRS, MIE) • • Negative HIV test at screening, with the following exception: • - Individual with a positive HIV test at screening are eligible provided, prior to • enrollment, they are stable on antiretroviral therapy for at least 4 weeks, have a • CD4 count □ 200/µL, have an undetectable viral load, and have not had a history • of opportunistic infection attributable to AIDS within the last 12 months. • • Adequate hematologic function (unless attributable to the underlying disease) • defined as follows: • – Hemoglobin □ 8.0 g/dL (□ 80 g/L), without packed RBC transfusion during 7 • days before first treatment • – ANC □ 1.0 □ 109 • /L (□ 1000/□L) • • Platelet count □50 □ 109 • /L (□50,000/□L), without a transfusion in the week prior to • starting study treatment • • Adequate renal function, defined as an estimated creatinine clearance □30 mL/min • • For female participants of childbearing potential: agreement to remain abstinent • (refrain from heterosexual intercourse) or use contraception, and agree to refrain • from donating eggs,

Principali criteri di esclusione:	• Pregnancy or breastfeeding, or intention of becoming pregnant during the study or • within 3 months after the final dose of tocilizumab, 2 months after the final dose of • glofitamab, whichever is longer. • Female participants of childbearing potential must have a negative serum • pregnancy test result (minimum sensitivity, 25 mIU/mL) within 24 hours prior to • Day 1 of Cycle 1 prior to initiating study treatment. • • Leukemic, non-nodal MCL • History of severe allergic or anaphylactic reactions to humanized or murine • monoclonal antibodies (or recombinant antibody-related fusion proteins) or known • sensitivity or allergy to murine products • • Contraindication to obinutuzumab or rituximab, and either bendamustine or • lenalidomide • • Prior treatment with glofitamab or other bispecific antibodies targeting both CD20 • and CD3 • • Prior treatment with CAR-T cell therapy • • Treatment with systemic therapy or BTK inhibitors, or any investigational agent for • the purposes of treating cancer within 2 weeks or 5 half-lives (whichever is the • shorter) prior to first study treatment • • Primary or secondary CNS lymphoma at the time of recruitment or history of CNS • lymphoma • • Current or history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or • neurodegenerative disease • – Participants with a history of stroke who have not experienced a stroke or • transient ischemic attack within the past 2 years and have no residual • neurologic deficits, as judged by the investigator, are allowed • • Any of the following abnormal laboratory values, unless abnormal laboratory values • are associated with the underlying lymphoma per the investigator: • – AST or ALT □ 2.5 □ upper limit of normal (ULN) • – Total bilirubin □ 1.5 □ ULN • – Participants with documented Gilbert disease may be enrolled if the total

	• bilirubin is □ 3 □ ULN • – INR or PT □ 1.5 □ ULN, or Quick percentage < 70% (if Quick percentage used in • lieu of time-based units for reporting PT), in the absence of therapeutic • anticoagulation • – PTT or aPTT □ 1.5 □ ULN in the absence of therapeutic anticoagulation or a • lupus anticoagulant • • History of other malignancy that could affect compliance with the protocol or • interpretation of results, with the following exceptions: • – Participants with a history of curatively treated basal or squamous cell • carcinoma of the skin or in situ carcinoma of the cervix at any time prior to the • study are eligible • – Participants with low-grade, early-stage prostate cancer (Gleason score 6 or • below, Stage 1 or 2) with no requirement for therapy at any time prior to study • are eligible • Participants with any other malignancy appropriately treated with curative • intent and the malignancy has been in remission without treatment for □ 2 years • prior to enrollment are eligible • – Participants receiving adjuvant endocrine therapy for non-metastatic, hormone • receptor□positive breast cancer for □ 2 years prior to enrollment are eligible • • Significant or extensive cardiovascular disease such as New York Heart Association • Class III or IV cardiac disease or Objective Assessment Class C or D, myocardial • infarction within the last 6 months, unstable arrhythmias, or unstable angina • • Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection • (excluding fungal infections of nail beds) at study enrollment or any major episode of • infection (as evaluated by the investigator) within 4 weeks prior to the first study • treatment • • Suspected or latent tuberculosis (confirmed by positive interferon-γ release assay) • • Positive test results for hepatitis B virus (HBV) infection (defined as positive • hepatitis B surface antigen [HbsAg] serology)

	• – Participants with occult or prior HBV infection (defined as negative HbsAg and • positive hepatitis B core antibody [HbcAb]) may be included if HBV DNA is • undetectable, provided that they are willing to undergo DNA testing on Day 1 of • every cycle and every 12 weeks for at least 12 months after the last cycle of • study treatment and appropriate antiviral therapy • • Positive test results for hepatitis C virus (HCV) antibody • – Participants who are positive for HCV antibody are eligible only if PCR is • negative for HCV RNA • • For participants with unknown HIV status, HIV testing will be performed at • screening if required by local regulations • • Known or suspected chronic active Epstein-Barr viral infection • • Known or suspected history of HLH • • Known history of progressive multifocal leukoencephalopathy (PML) • • Adverse events from prior anti-cancer therapy that have not resolved to Grade 1 or • better (with the exception of alopecia and anorexia) • • Administration of a live, attenuated vaccine within 4 weeks before first study • treatment administration or anticipation that such a live, attenuated vaccine will be • required during the study • • Prior solid organ transplantation • • Prior allogeneic stem cell transplant • • Eligibility for stem cell transplantation (SCT). Participants achieving a CR during • the course of the study should not intend to proceed to autologous hematopoietic • stem cell transplant • • Active autoimmune disease requiring treatment • – Participants with a history of autoimmune-related hypothyroidism on a stable • dose of thyroid-replacement hormone may be eligible • – Participants with controlled Type 1 diabetes mellitus who are on an insulin • regimen are eligible for the study • – Participants with a history of autoimmune hepatitis, systemic lupus • erythematosus, inflammatory bowel disease, vascular thrombosis associated

	• with antiphospholipid syndrome, Wegener granulomatosis, Sjögren syndrome, • multiple sclerosis, or glomerulonephritis will be excluded • – Participants with a history of immune thrombocytopenic purpura, autoimmune • hemolytic anemia, Guillain-Barré syndrome, myasthenia gravis, myositis, • rheumatoid arthritis, vasculitis, or other autoimmune diseases will be excluded • unless they have not required systemic therapy in the last 12 months • • Prior treatment with systemic immunosuppressive medications (including, but not • limited to, cyclophosphamide, azathioprine, methotrexate, thalidomide, and • anti-tumor necrosis factor agents), within 2 weeks or five half-lives (whichever is • shorter) prior to first dose of study treatment • • Corticosteroid therapy within 2 weeks prior to first dose of study treatment, with the • following exceptions: • – Corticosteroid treatment 10 mg/day prednisone or equivalent within 2 weeks • prior to the first dose of study treatment is permitted • – Administration of acute, low-dose corticosteroids to treat cancer symptoms or • side effects of treatment is permitted • – The use of inhaled corticosteroids is permitted • – The use of mineralocorticoids for management of orthostatic hypotension is • permitted • – The use of physiologic doses of corticosteroids for management of adrenal • insufficiency is permitted • • Recent major surgery (within 4 weeks before the first study treatment) other than for • diagnosis • • Clinically significant history of cirrhotic liver disease • • Any other diseases, metabolic dysfunction, physical examination finding, or clinical • laboratory finding giving reasonable suspicion of a disease or condition that • contraindicates the use of an investigational drug or that may affect the • interpretation of the results or renders the patient at high risk from treatment • complications

	• Positive SARS-CoV-2 PCR test within 7 days prior to enrollment
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