A.O. S. Croce e Carle di Cuneo

Titolo:	A Randomized, Open-Label, Controlled Phase 3 Study Comparing Daratumumab, Lenalidomide and Dexamethasone Induction followed by Linvoseltamab Versus continued Daratumumab, Lenalidomide, and Dexamethasone in Newly Diagnosed Transplant Ineligible Multiple Myeloma Patients (Studio EMN39)
Patologia:	MM
Tipo di Studio:	Interventistico farmacologico
Fase:	III
Principali criteri di inclusione:	1. Participants must have confirmed diagnosis of symptomatic MM per IMWG criteria. 2. Participants must not be considered a candidate for high-dose chemotherapy (HDT) and ASCT due to: • advanced age with or without comorbidities or • for patients aged 18-69 the presence of significant comorbidities that are likely to have a negative impact on tolerability of HDT-ASCT The reason(s) for transplant ineligibility must be provided by the investigator. 3. Participants must have measurable disease, as defined by at least 1 of the following (according to the 2016 IMWG response criteria): • Serum monoclonal protein level ≥1 g/dL • Quantitative immunoglobulin levels of ≥1 g/dL (Immunoglobulin A [IgA] and immunoglobulin D [IgD] myeloma only). Note: for IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments. • Urinary M-protein level of ≥200 mg over a 24-hour period • Involved serum FLC level ≥10 mg/dL, along with an abnormal FLC ratio in patients with FLC only measurable myeloma NOTE: All attempts should be made to establish measurable disease at screening based on blood or urine central laboratory results. Under exceptional circumstances and with the sponsor's approval, local laboratory results of blood, urine M-protein measurements, and sFLC may be used to determine measurable disease if the results are ≥25% above the thresholds for measurability. Central laboratory results are still to be obtained prior to the start of administration of study treatment as a reference for response assessment.

	4. ECOG performance status of 0, 1, or 2. 5. Participants must have clinical laboratory values meeting the below criteria. These laboratory values must be evaluated during screening and be re-evaluated within 72 hours prior to the first dose and the patient must meet all criteria at both assessments. If one or more criteria are not met 72 hours prior to dosing, 1 repeat of laboratory testing is permitted. • ANC ≥1,000 cells/mm3 (1 x 109 cells/L) without growth factor support within 7 days for G-CSF and within 14 days for pegylated-G-CSF of the lab assessment. • Hemoglobin ≥7.5 g/dL (≥4.65 mmol/L) without red blood cell transfusions within 7 days of the lab assessment. • Platelet counts of ≥75,000 cells/mm3 for participants who have bone marrow plasmacytosis of <50%, or ≥50,000 cells/mm3 for participants who have bone marrow plasmacytosis of ≥50%. A participant may not have received a platelet transfusion or thrombopoietin receptor agonist within 7 days of the lab assessment. • Serum creatinine clearance by MDRD (Modification of Diet in Renal Disease) ≥30 mL/min. A participant with a creatinine clearance by MDRD who does not meet eligibility criteria may be considered for enrollment if a measured creatinine clearance, based on 24-hour urine collection or another reliable method is ≥30 mL/min. • Total bilirubin ≤2 times the institutional upper limit of the normal values (IULN), with the exception of participants that have known or suspected Gilbert's syndrome, (in which case direct bilirubin ≤2.0 x ULN is required). • Total AST, ALT, and ALP ≤3 X ULN. • Serum calcium corrected for albumin ≤14 mg/dL (≤3.5 mmol/L) or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L). 6. Be willing and able to comply with clinic visits and study-related procedures, including serial bone marrow evaluations. 7. Be willing to be hospitalized or remain in close proximity (within 30 minutes) to the hospital at minimum after step-up dose 1 if randomized to the experimental arm. 8. Due to the embryo-fetal risk associated with IMiDs, all participants must adhere to the global PPP or local PPP/REMS program for lenalidomide. 9. Able to understand and complete study-related questionnaires
Principali criteri di esclusione:	1. IMWG Frailty Index of ≥2 (i.e. frail patients) with the exception of participants who have a score of 2 and are frail based on age alone. Participants who have a frailty score of 2 based on age alone will be capped at 10% of the total study population.

	2. Participants who defer transplant due to personal preference (who would otherwise be candidates for transplant based on age and absence of comorbid conditions that would preclude transplant candidacy). 3. Participants with non-secretory MM, active plasma cell leukemia defined as either having 5% of peripheral white blood cells comprised of CD138+ plasma cells, known light-chain (AL) amyloidosis in the presence of a concurrent diagnosis of myeloma, any other form of amyloidosis, Waldenström macroglobulinemia (lymphoplasmacytic lymphoma), or known POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes). 4. Any prior therapy for monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or MM, with the exception of: • Focal Radiation, such as on an emergency basis for a presentation with spinal cord compression, or on a palliative basis to improve pain control. A washout period of at least 2 weeks for radiation therapy should be met prior C1D1. Radiotherapy within 14 days of C1D1 on measurable soft tissue plasmacytoma(s) is not permitted even in the setting of palliation for symptomatic management. • A short course of corticosteroids for emergency use (maximum dexamethasone equivalent 40mg/day for 4 days) will be allowed up to 5 days prior to C1D1, provided that the participant remains eligible based on the measurable disease criteria defined above. 5. Participants who have received or are receiving any investigational agent or cell therapy with known or suspected activity against MM (or another plasma cell disorder), or those whose AEs due to agents administered earlier (such as radiation and/or corticosteroids) have not recovered to a severity of grade 0 or grade 1. 6. Participants who have undergone any major surgery within 4 weeks prior to C1D1, with the following exceptions: • Vertebroplasty and/or kyphoplasty, which must have been performed at least 1 week prior to C1D1. • Planned elective minor surgery unrelated to the participant's diagnosis of myeloma, such as hernia repair, may be allowed, at the discretion of the Principal Investigators and Study Sponsor, as long as it was performed at least 2 weeks prior to C1D1, and participants have fully recovered from this procedure. 7. Participants who have known central nervous system (CNS) or meningeal involvement with MM or known or

	suspected progressive multifocal leukoencephalopathy (PML), a history of a neurocognitive condition or CNS movement disorder, OR a history of seizure, transient ischemic attack (TIA), stroke or seizure within 12 months prior to study C1D1. 8. Participants who have uncontrolled intercurrent illness including, but not limited to: • ongoing or active viral, fungal, or bacterial infection, requiring systemic antimicrobial therapy • Active autoimmune disease or a documented history of autoimmune disease with the exception of vitiligo, type I diabetes, and prior autoimmune thyroiditis that is currently euthyroid based on clinical symptoms and laboratory testing • symptomatic congestive heart failure (for example, NYHA Class III or IV Heart Failure; New York Heart Association (NYHA) Classification, 2018) • cardiac dysfunction evidenced by ejection fraction <40% by echocardiogram or multi-gated acquisition scan (Bingham & Hachamovitch, 2008) • angina pectoris • hypertension (defined as an average systolic blood pressure >159 mm Hg or diastolic >99 mm Hg, despite optimal treatment) • cardiac arrhythmia (except clinically insignificant, asymptomatic bradycardia) • Has COPD with an FEV1 <50% of predicted. (FEV1 testing is required for participants suspected of having COPD). • asthma (moderate or severe persistent asthma within the past 2 years, or current uncontrolled asthma of any classification) • diabetes (HbA1C averaging >8% in the 6 months prior to C1D1) • psychiatric condition or diagnosis (alcohol or drug abuse, severe dementia, or altered mental status), or social situations that would limit compliance with study requirements, in the opinion of the investigators or Sponsor. 9. History of myocardial infarction within the previous 12 months prior to C1D1. 10. History of severe allergic reaction attributed to any study drug or excipient (ie, monoclonal antibodies and/or their excipients) used to treat indications other than MM. A “severe allergic reaction” is defined for this purpose as requiring hospitalization and/or treatment with epinephrine. Prior infusion reactions with monoclonal antibody-based therapeutics will not be considered evidence of an allergic reaction.

	11. Known contraindications to the use of daratumumab or lenalidomide per local prescribing information. 12. Known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of lenalidomide (eg, gastric bypass, lap band, or other gastric procedures that would alter absorption); delivery of lenalidomide via nasogastric tube or gastrostomy tube is not allowed. 13. Participants who required plasmapheresis within 4 weeks from C1D1. 14. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), or another uncontrolled infection (such as cytomegalovirus [CMV]). Additional guidelines for HIV, HBV, and HCV are: • Participants with HIV, without history of AIDS defining condition, who have controlled infection are permitted. • Participants with HBV: defined by a positive test HBsAg (seropositive for hepatitis B). • Participants with resolved infection must be screened using RT-PCR measurement of HBV-DNA levels. Those who are RT-PCR positive will be excluded. • Participants with serologic findings suggestive of HBV vaccination AND a known history of prior HBV vaccination, do not need to be tested for HBV-DNA by RT-PCR. • Participants who are HCV antibody positive who have controlled infection are permitted. 15. Participants will be excluded if they have any of the following malignancies: • Myelodysplastic syndrome or B cell malignancy (other than multiple myeloma) • Any history of malignancy that is considered at high risk of recurrence requiring systemic therapy, other than multiple myeloma • Prior or concurrent malignancy within 24 months prior to the date of randomization (other than multiple myeloma) • The only allowed exceptions are malignancies adequately treated within the last 24 months that are considered cured • Non-muscle invasive bladder cancer (solitary Ta-papillary urothelial neoplasm of low malignancy or low grade, <3 cm, no carcinoma in situ) • Non-melanoma skin cancers treated with curative therapy or localized melanoma treated with curative surgical resection alone • Noninvasive cervical cancer • Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ or history of localized breast cancer (anti-hormonal therapy is permitted)

	• Localized prostate cancer (M0, N0) with a Gleason Score ≤7a, treated locally only (radical prostatectomy/radiation therapy/focal treatment) • Other malignancy that is considered cured with minimal risk of recurrence are permitted following consultation with and approval by the sponsor's medical monitor. 16. Investigational, live or live attenuated, or replication-competent viral vector vaccine within 28 days prior to first study treatment. 17. History of allogeneic hematopoietic stem cell transplantation or solid organ transplant at any time. 18. Known hypersensitivity to both allopurinol and rasburicase. 19. Unable or unwilling to undergo antithrombotic prophylactic treatment as determined by investigator. 20. Members of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor. 21. Pregnant or breastfeeding females. 22. Females of childbearing potential (FOCBP)* or sexually active males who are unwilling to practice highly effective contraception prior C1D1, during the study, and for at least 6 months after the last dose. For males, sperm donation is prohibited during the study and for at least 6 months after the last dose of any study drug. Highly effective contraceptive measures include: • stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; • intrauterine device (IUD); intrauterine hormone-releasing system (IUS); • bilateral tubal occlusion/ligation; • vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the FOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure); and/or • sexual abstinence†, ‡. Pregnancy testing and contraception are required for FOCBP. Pregnancy testing and contraception are not required for females who are post-menopausal or permanently sterile. FOCBP must agree to not donate eggs (ova, oocytes) for the purpose of assisted reproduction during the study and for at least 6 months after the last dose of any study drug. *FOCBP are defined as females who are fertile following menarche until becoming postmenopausal, unless

	permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
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