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TITEL

A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared With CyBorD Alone in Newly Diagnosed Systemic AL Amyloidosis.

INDICATIE

Adult subjects age 18 and older with newly diagnosed AL amyloidosis are eligible for the study. Diagnosis will be based on histopathological or electron microscopy criteria, one or more organs need to be affected, and disease must be measurable (by free light chain criteria or serum monoclonal protein [M-protein]). Eligible subjects will have an ECOG performance score of 0, 1, or 2 and adequate organ function. Key exclusion criteria include previous or current diagnosis of symptomatic multiple myeloma, evidence of significant cardiovascular conditions, any form of non-AL amyloidosis, or planned stem cell transplant during first 6 cycles of protocol therapy.

SYNOPSIS

This is a randomized, open-label, active-controlled, multicenter Phase 3 study in subjects with newly diagnosed amyloid light chain amyloidosis. Approximately 360 subjects will be stratified by cardiac stage based on the Mayo Clinical Cardiac Staging System (Dispenzieri 201410; Palladini 201634) (Stages I, II, and IIIa) (Attachment 15), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (creatinine clearance [CrCl] ≥60 mL/min or CrCl <60 mL/min) and then assigned to receive either CyBorD or CyBorD in combination with daratumumab. Subject participation will include a Screening Phase, a treatment Phase, a Post-Treatment Observation Phase, and a Long-term Follow-up Phase.
Given the potential safety concern with regards to the use of IV daratumumab in the amyloidosis population (ie, volume overload), this study will utilize the daratumumab SC co-formulation. Although the risk of volume overload is predicted to be lower with SC daratumumab than with IV infusion, patients with newly diagnosed AL amyloidosis may still develop adverse events (AEs) attributable to hypervolemia (for example, dyspnea, peripheral edema, etc) secondary to amyloid-induced cardiac or renal insufficiency. Additionally, daratumumab has not been co-administered with CyBorD. Therefore, prior to the start of the randomized portion of the study, a safety run-in will be conducted. Dosing of these subjects will be staggered so that no subject will receive their first dose sooner than 48 hours after the previously enrolled subject. Safety evaluation will be performed by the sponsor (and external academic hematologists) after at least 10 subjects have received at least 1 cycle of treatment If no safety signal is observed, particularly in regard to volume overload, the randomized portion of the study will begin. Once the randomized portion of the study begins, subjects in Treatment Arm B (CyBorD plus daratumumab) will be observed for at least 6 hours after the end of study drug administration during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive administrations.
The safety run-in data have been assessed by the Study 54767414AMY3001 Steering Committee members consisting of 4 academic hematologists with expertise in AL amyloidosis. The Steering Committee members concur that the combination of daratumumab with CyBorD appears to be safe and tolerable for the first 15 subjects with newly diagnosed AL amyloidosis treated in the safety run-in of Study 54767414AMY3001 and support the start of the randomized portion of the study.

In the randomized portion of the study, subjects randomized to Treatment Arm A will receive study treatment with CyBorD. All treatment cycles are 4 weeks (28 days) in length. CyBorD will be administered for a maximum of 6 cycles (24 weeks).
Subjects randomized to Treatment Arm B will receive CyBorD plus daratumumab at a fixed dose of 1800 mg. A maximum of 6 cycles (24 weeks) of CyBorD plus daratumumab will be administered. After Cycle 6, subjects will continue to receive daratumumab as monotherapy on Day 1 of subsequent 28-day cycles until disease progression, start of subsequent therapy, or a maximum of 2 years from the start of the study.

INCLUSIE CRITERIA

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

- 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) or older.
- Histopathological diagnosis of amyloidosis based on detection by IHC and polarizing light microscopy of green bi-refringent material in congo red-stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance (please refer to Section 9.1.2.1).

Considerations for specific populations where other types of amyloidosis may be encountered:

  - For male subjects 70 years of age or older who have cardiac involvement only, and subjects of African descent (black subjects), mass spectrometry typing of AL amyloid in a tissue biopsy is recommended to rule out other types of amyloidosis such as age-related amyloidosis or hereditary amyloidosis (ATTR mutation)

- Measurable disease of amyloid light chain amyloidosis as defined by at least ONE of the following:
  - serum M-protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation (IFE) performed at a central laboratory),
  - serum free light chain ≥5.0 mg/dL with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥5 mg/ dL.

Note: Measurable disease by urine Bence-Jones proteinuria is not sufficient for study enrollment.

- One or more organs impacted by AL amyloidosis according to consensus guidelines
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2
  Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:
  - Absolute neutrophil count ≥1.0 × 109/L;
  - Hemoglobin level ≥8.0 g/dL (≥5 mmol/L); red blood cell transfusion allowed until 7 days before randomization
  - Platelet count ≥50 × 109/L; Platelet transfusions are acceptable without restriction during the Screening period
  - Alanine aminotransferase level (ALT) ≤2.5 times the ULN
  - Aspartate aminotransferase (AST) ≤2.5 times the ULN
  - Total bilirubin level ≤1.5 × ULN except for subjects with Gilbert syndrome, in which case direct bilirubin ≤2 × ULN
  - Estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m2. Please note the eGFR is measured by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see Attachment 5 for details)

- Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse (if this is the preferred and usual lifestyle of the subject) or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device, hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing and continue for 1 year after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy.
- During the study and for 1 year after stopping cyclophosphamide or 3 months after receiving the last dose of daratumumab, whichever is longer, a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction.
- A man who is sexually active with a woman of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control; eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository during and up to 6 months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer. All men must also not donate sperm during the study and for 6 months after discontinuation of cyclophosphamide or 3 months after discontinuation of daratumumab, whichever is longer.
- A woman of childbearing potential must have a negative serum or urine pregnancy test (serum preferred) result within 14 days prior to randomization. For requirements during the Treatment Phase, please see the Time and Events Schedule (Table 1).
- Each subject, or legally acceptable representative, must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subjects must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

EXCLUSIE CRITERIA

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

- Prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38, with the exception of 160 mg dexamethasone (or equivalent corticosteroid) maximum exposure prior to randomization
- Previous or current diagnosis of symptomatic multiple myeloma, including the presence of lytic bone disease, plasmacytomas, ≥60% plasma cells in the bone marrow, or hypercalcemia
- Evidence of significant cardiovascular conditions as specified below:
    - NT-ProBNP >8500 ng/L
    - New York Heart Association (NYHA) classification IIIB or IV heart failure
    - Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzyme elevation and ECG changes) or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy

    - Inpatient admission to a hospital for unstable angina or myocardial infarction within the last 6 months prior to first dose or percutaneous cardiac intervention with recent stent within 6 months or coronary artery bypass grafting within 6 months
    - For subjects with congestive heart failure, cardiovascular-related hospitalizations within 4 weeks prior to randomization
    - Subjects with a history of sustained ventricular tachycardia or aborted ventricular fibrillation or with a history of atrioventricular nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but not placed (Subjects who do have a pacemaker/ICD are allowed on study)
    - Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >500 msec. Subjects who have a pacemaker may be included regardless of calculated QTc interval.
    - Supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension, defined as a decrease in systolic blood pressure upon standing of >20 mmHg despite medical management (eg, midodrine, fludrocortisones) in the absence of volume depletion
- Planned stem cell transplant during the first 6 cycles of protocol therapy are excluded. Stem cell collection during the first 6 cycles of protocol therapy is permitted
- History of malignancy (other than AL amyloidosis) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).
- Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.
- Moderate or severe persistent asthma within the past 2 years (see Attachment 6), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).
- Know to be seropositive for human immunodeficiency virus (HIV).
- Any of the following:
    - Known to be seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie, subjects who are positive for antibodies to hepatitis B core antigen [antiHBc] and/or antibodies to hepatitis B surface antigen [antiHBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (antiHBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
    - Known to be seropositive for hepatitis C (except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).
- Grade 2 sensory or Grade 1 painful peripheral neuropathy.
- Known hypersensitivity or contraindication to any of the study drugs including bortezomib, boron, mannitol, or cyclophosphamide or any of its metabolites.

- Concurrent medical condition or disease (eg, active systemic infection) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard for participating in this study.
- Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis.
- Known allergies, hypersensitivity, or intolerance to monoclonal antibodies, hyaluronidase, human proteins, or their excipients (refer to IB), or known sensitivity to mammalian-derived products.
- Known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder) or the subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise their well-being) or that could prevent, limit, or confound the protocol-specified assessments.
- Woman who is pregnant or breastfeeding or planning to become pregnant while enrolled in this study or within 1 year after discontinuation of cyclophosphamide or 3 months following discontinuation of daratumumab, whichever is longer
- Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before Cycle 1 Day 1.
- Major surgery within 2 weeks before Cycle 1 Day 1, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study treatment administration.
  Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.
- Subjects who are taking CYP3A4 inducers must discontinue their use at least 5 half-lives prior to the first dose of study treatment.

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study treatment is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Subjects may be rescreened upon approval by the sponsor.