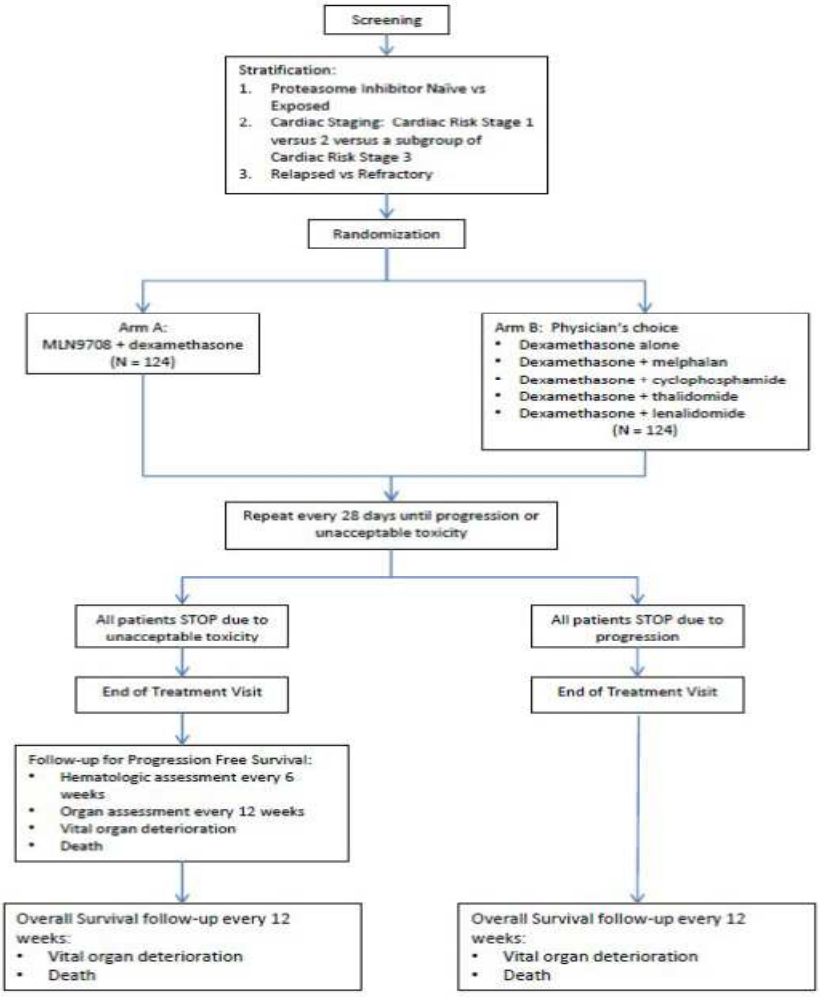
SAMENVATTING C16011

TITEL

A Phase 3, Randomized, Controlled, Open-Label, Multicenter, Safety and Efficacy Study of Dexamethasone Plus MLN9708 or Physician's Choice of Treatment Administered to Patients With Relapsed or Refractory Systemic Light Chain (AL) Amyloidosis

DOEL

- To determine whether dexamethasone plus MLN9708 improves hematologic response (PR + VGPR + CR) versus a physician's choice of a chemotherapy regimen as selected from the list of offered treatment options in patients diagnosed with relapsed or refractory AL amyloidosis.
- To determine whether dexamethasone plus MLN9708 improves 2-year vital organ (that is, heart or kidney) deterioration and mortality rate versus a physician's choice of a chemotherapy regimen as selected from the list of offered treatment options in patients diagnosed with relapsed or refractory AL amyloidosis. Cardiac deterioration is defined as the need for hospitalization for heart failure. Kidney deterioration is defined as progression to end-stage renal disease (ESRD) with the need for maintenance dialysis or renal transplantation.



INCLUSIECRITERIA

To be eligible for this study, a prospective patient must meet EACH of the following

1. Male or female patients 18 years or older.
2. Biopsy-proven diagnosis of AL amyloidosis according to the following standard criteria:

a. Histochemical diagnosis of amyloidosis, as based on tissue specimens with Congo red staining with exhibition of an apple-green birefringence

b. If clinical and laboratory parameters insufficient to establish AL amyloidosis or in cases of doubt, amyloid typing may be necessary

3. Measurable disease as defined by serum differential free light chain concentration(dFLC, difference between amyloid forming [involved] and nonamyloid forming [uninvolved] free light chain [FLC]) ≥ 50 mg/L.
4. Objective, measurable major (cardiac or renal) organ amyloid involvement as defined as follows (amyloid involvement of at least 1 required):

a. Cardiac involvement is defined as the presence of a mean left ventricular wall thickness on echocardiogram greater than 12 mm in the absence of a history of hypertension or valvular heart disease, or in the presence of unexplained low voltage (< 0.5 mV) on the electrocardiogram)

b. Renal involvement is defined as proteinuria (predominantly albumin) > 0.5 g/day in a 24- hour urine collection

Note: Amyloid involvement of other organ systems is allowed, but not required.

5. Must be relapsed or refractory after 1 or 2 prior therapies.

For this protocol, relapsed is defined as PD documented more than 60 days after last dose; refractory is defined as documented absence of hematologic response or hematologic progression on or within 60 days after last dose of prior therapy.

a. Patient may not be refractory to proteasome inhibitor therapy

b. Given that the physician may select from an offered list of regimens to treat a specific patient, the patient may be refractory to an agent/s listed within the list of offered treatment choices

c. Must have recovered (ie, ≤ Grade 1 toxicity or patient's baseline status) from the reversible effects of prior therapy

d. If a patient has received a transplant as his/her first-line therapy, he/she must be at least 3 months posttransplantation and recovered from the side effects of the stem cell transplant

6. Patient must meet criteria for 1 of the following AL Amyloidosis Risk Stages (as defined by NT-proBNP cut off of < 332 pg/mL and troponin T cut-off of 0.035 ng/mL as thresholds):

a. Stage 1: both NT-proBNP and troponin T under threshold

b. Stage 2: either NT-proBNP or troponin T [but not both] over threshold;c. Stage 3: both NT-proBNP and troponin T over threshold (but NT-proBNP < 8000 pg/mL)

7. ECOG Performance Status ≤ 2
8. Clinical laboratory values:

a. Absolute neutrophil count □□1000/□L

b. Platelet count □□75,000/□L

c. Total bilirubin ≤ 1.5 □□ULN

d. Alkaline phosphatase ≤ 5 □□ULN,

e. ALT or AST ≤3 □□ULN
f. Calculated creatinine clearance ≥ 30 mL/min

EXCLUSIECRITERIA
Prospective patients will be excluded from this study if they meet ANY of the following criteria:
1. Amyloidosis due to mutations of the transthyretin gene or presence of other non-AL amyloidosis.
2. Female patients who are lactating, breastfeeding, or pregnant.
3. Medically documented cardiac syncope, uncompensated NYHA Class 3 or 4 congestive heart failure , myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant repetitive ventricular arrhythmias despite antiarrhythmic treatment, or severe orthostatic hypotension or clinically important autonomic disease.
4. Clinically overt multiple myeloma, including monoclonal BM plasma cells ≥10% to ≥ 30%, and at least 1 of the following:
a. Bone lesions
b. Hypercalcemia, defined as a calcium of > 11 g/dL
5. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or GI procedure that could interfere with the oral absorption or tolerance of treatment.
6. Requirement for other concomitant chemotherapy, immunotherapy, radiotherapy, or any ancillary therapy considered to be investigational or which would be considered as a treatment of AL amyloidosis. However, patients may be on chronic steroids (maximum dose 20 mg/day prednisone or equivalent if they are being given for disorders other than amyloidosis (eg, adrenal insufficiency, rheumatoid arthritis, etc.).
7. Comorbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
8. Ongoing or active infection, known HIV positive, active hepatitis B or C infection.
9. Psychiatric illness/social situations that would limit compliance with study requirements.
10. Known allergy to boron, MLN9708, any of the study treatments, their analogues, or excipients.
11. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort within 14 days before the first dose of study treatment.
12. Diagnosed or treated for another malignancy within 5 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.