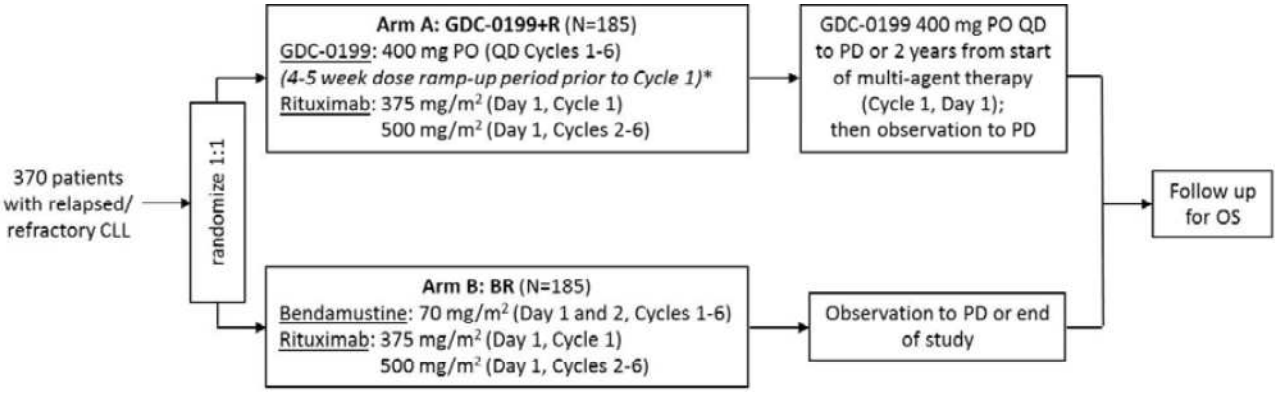
# SAMENVATTING GO28667 MURANO

**Titel**
A multicenter, phase III open-label,Randomized study in Relapsed/refractory patients with Chronic lymphocytic leukemia to Evaluate the benefit of gdc-0199 (abt-199) plus rituximab compared with Bendamustine plus rituximab

**Indicatie**
Relapsed/refractory Chronic Lymphocytic Leukemia

**Studieopzet/Behandelplan**




**Inclusion criteria**

1. Age ≥ 18 years.
2• Diagnosis of CLL that meets published diagnostic criteria (Hallek et al. 2008).
Patients must have peripheral blood B-lymphocyte counts which clonally express CD5, CD19/20, and CD23 and are either kappa or lambda light-chain-restricted. Pro-lymphocytes may comprise no more than 55% of total circulating lymphocytes. At initial diagnosis of CLL (ie, prior to front-line treatment), the peripheral lymphocyte count must have been > 5000/mm3. Patients must meet the following criteria for relapsed or refractory CLL (per the iwCLL guidelines [Hallek et al. 2008]):
– Relapsed disease: a patient who previously achieved a CR or PR, but after a period of 6 months or more demonstrates evidence of progression;
– Refractory disease: treatment failure or disease progression within 6 months of the last anti-leukemia therapy.
3• Previously treated with at least one but not more than three lines of therapy (a line of therapy is defined as completing at least two cycles of treatment for a given line of therapy), including at least one prior standard chemotherapy-containing regimen according to current guidelines (Appendix 8).
4. For patients with 17p deletion, previously treated with at least one but not more than three lines of therapy, including at least one prior standard chemotherapy-containing regimen according to current guidelines OR at least one prior alemtuzumabcontaining therapy.
4• Patients previously treated with bendamustine only if their duration of response was ≥ 24 months.
5• Patient requires treatment in the opinion of the investigator.
6• Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 1
7• Adequate BM function independent of growth factor or transfusion support, per local laboratory reference range at screening as follows:
– platelet count ≥ 75 000/mm3;
– absolute neutrophil count (ANC) ≥ 1000/mm3 unless cytopenia is clearly due to marrow involvement of CLL;
– total hemoglobin ≥ 9 g/dL (without transfusion support within 2 weeks of screening);
– if any of the above-mentioned cytopenias are present, there should be no evidence of myelodysplastic syndrome (MDS) or hypoplastic BM.
8• Adequate renal and hepatic function

9• Female patients must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test a partner who is surgically sterile or postmenopausal (for at least 1 year) or who is taking hormonal contraceptives

**Exclusion criteria**

1• Transformation of CLL to aggressive NHL (eg, Richter's transformation, prolymphocytic leukemia, or DLBCL) or CNS involvement by CLL.
2• Undergone an allogeneic stem cell transplant.
3• Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia.
4• History of intolerance to prior bendamustine treatment (defined as toxicity requiring permanent discontinuation of bendamustine) or other contraindication to bendamustine treatment.
5• History of severe (ie, requiring permanent discontinuation of prior rituximab therapy) prior allergic or anaphylactic reactions to rituximab.
6• Known HIV-positivity
7. Positive hepatitis serology (serology testing required at screening
8• Requires the use of warfarin (due to potential drug - drug interactions that may potentially increase the exposure of warfarin). Patients may be eligible if able to be taken off warfarin and started on an alternative anticoagulant.
9• Received an anti-CLL monoclonal antibody within 8 weeks prior to the first dose of study drug.
10• Received any of the following agents within 14 days prior to the first dose of study drug, or has not recovered to less than Grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
– any anti-cancer therapy including chemotherapy or radiotherapy and steroid therapy for anti-neoplastic intent;
– investigational therapy, including targeted small-molecule agents.
11• Received *potent* CYP3A4 inhibitors (such as fluconazole, ketoconazole, and clarithromycin) within 7 days prior to the first dose of GDC-0199 (see Appendix 9).
12• Received potent CYP3A4 inducers (such as rifampin, carbamazepine, phenytoin, St. John's Wort) within 7 days prior to the first dose of GDC-0199 (see Appendix 9).
13• History of prior GDC-0199 treatment.
14• Consumed grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of GDC-0199.
15• A cardiovascular disability status of New York Heart Association Class ≥ 3
16• A significant history of renal, neurologic, psychiatric, endocrine, metabolic, immunologic, cardiovascular, or hepatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in this study or interpretation of study outcomes.
17• *Major surgery within 30 days prior to the first dose of GDC-0199.*
18• A female patient who is pregnant or breast-feeding.
19• History of prior other malignancy that could affect compliance with the protocol or interpretation of results with the exception of the following:
– curatively treated basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of the cervix at any time prior to study;
– other cancers not specified above which have been curatively treated by surgery and/or radiation therapy from which patient is disease-free for ≥ 5 years without further treatment.
20• Malabsorption syndrome or other condition that precludes enteral route of administration.
21• Known allergy to both xanthine oxidase inhibitors and rasburicase.
22• Evidence of other clinically significant uncontrolled condition(s) including, but not limited to, uncontrolled systemic infection (viral, bacterial, or fungal).
23• Vaccination with a live vaccine within 28 days prior to randomization.