ALTAMIRA

Acalabrutinib and rituximab in elderly patients with untreated mantle cell lymphoma

PROTOCOL NUMBER:	NLG-MCL8
STUDY DRUG:	Acalabrutinib, Rituximab
EUDRACT NUMBER:	2018-001850-80
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PROTOCOL:	Version 3.1 2021-10-13

1.0 STUDY SYNOPSIS

Study Title:	ALTAMIRA
Protocol Number:	NLG-MCL8
Study Drug:	ACALABRUTINIB (ACP-196), RITUXIMAB
Phase:	Phase 2
Study Centers:	Patients will be enrolled in approximately 20 centers in Sweden, Norway, Denmark, Finland and South Korea
Study Objectives:	Primary Objective(s): To evaluate progression-free survival with acalabrutinib-rituximab in patients with untreated mantle cell lymphoma, compared to data from the NLG-MCL4 trial Secondary Objective(s): • To evaluate: • Complete remission rate (CR) • Molecular remission rate (MRR) by PCR • Overall response rate (ORR) • Progression-free survival (PFS) • Duration of response (DOR) • Duration of molecular remission • Overall survival (OS) • Safety • CR, MRR and ORR in *TP53*-mutated MCL As an exploratory endpoint, we will also compare PFS, OS to the ibrutinib-rituximab arm of the phase 3 ENRICH trial.
Study Design:	This is a phase II trial, with the aim of developing a chemotherapy-free regimen for untreated patients with MCL. Acalabrutinib, or ACP-196, is a next generation BTK inhibitor, more selective than ibrutinib, and without in vitro antagonism of anti-CD20 directed immunotherapies, indicating that its combination with

	rituximab may be more active than the combination of ibrutinib and rituximab (Barf et al., 2017; Wang et al., 2017). In this trial proposal, we will also assess the activity of this combination in comparison to a historical control of ibrutinib + rituximab, consisting of the experimental arm of ibrutinib + rituximab in the randomized ENRICH trial (EudraCT number 2015-000832-13), and data from our previous trial with R-bendamustine-lenalidomide (NLG-MCL4). The duration of treatment will be a minimum of 12 months. Patients in molecular remission in blood and bone marrow and in complete remission according to CT, will then stop acalabrutinib, but continue on rituximab for a maximum of 36 months. Patients that are MRD+ will be evaluated again every 6 months and continue on acalabrutinib for a maximum of 36 months. Patients without a molecular marker, that cannot be followed with MRD, will stop treatment if in CR with PET at 12 months, and be followed by PET-CT every 6 months for a maximum of 36 months. Patients who convert back to MRD positive after stopping acalabrutinib are reinstalled on acalabrutinib until progression. Patients with TP53 aberrations and/or blastoid histology, will monitor MRD but continue with treatment until progression regardless of MRD results. A planned interim analysis will be performed when 40 patients have undergone response assessment after 6 months, for futility and efficacy. If less than 16 of 40 patients obtain a CR, the trial will be stopped due to futility.

Efficacy and Safety Parameters:	• Progression free survival • Complete response rate at 6 months • Molecular remission rate by PCR • Overall response rate • Progression-free survival (median) • Response duration (median) • Duration of molecular remission (median) • Overall survival (median) • CR, MRR and ORR in *TP53*-mutated MCL • Safety, in terms of all grade 3-5 AE
Pharmacodynamic, Pharmacokinetic and Biomarker Parameters:	Not applicable
Sample Size:	As comparator, we will use our previous trial (NLG-MCL4), with rituximab, bendamustine and lenalidomide. This trial included 50 patients, with a median time of follow-up of 47 months. The median progression-free survival (PFS) is 42 months (95% CI 28.5–55.5; n events=30). To show an improvement in PFS with an HR of 0.67 (alpha 0.05, beta 0.2), 80 patients are needed.
Inclusion Criteria:	1. Age ≥60 years 2. Pathologically confirmed MCL (according to the 2016 WHO classification), with documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1 3. Stage II-IV, measurable by imaging and requiring treatment in the opinion of the treating clinician 4. No previous treatment for MCL (other than localised radiotherapy or 7-day pulse of steroids for symptom control) 5. ECOG performance status 0 – 2 6. Absolute neutrophil count (ANC) > 1.0 x 10^9 and platelet count >100 x 10^9, unless related to lymphoma - in this situation, the threshold for inclusion is ANC > 0.5 x 10^9 and platelet count > 50 x 10^9

	7. Creatinine clearance >30 ml/min (Cockcroft-Gault) 8. AST and/or ALT <3x ULN and/or total bilirubin <3x ULN 9. Able to give voluntary written informed consent 10. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib or for 12 months after last dose of rituximab, whichever is longer
Exclusion Criteria:	1. Patients considered fit enough to undergo autologous or allogeneic stem cell transplant for MCL 2. Major surgery within two weeks prior to day 1 of cycle 1 3. Patients who are unable to swallow capsules, or who have disease significantly affecting gastrointestinal function that would limit oral absorption of medication 4. Known serological positivity for HBV, HCV, HIV. Patients who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result. Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded. Patients who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded 5. Diagnosed with or treated for any other malignancy than MCL within 2 years prior to day 1 of cycle 1 (except basal cell carcinoma, cutaneous squamous cell carcinoma or any other in situ malignancy) 6. Active infection requiring treatment 7. Serious medical or psychiatric illness likely to interfere with participation in this clinical study 8. Concurrent treatment with another investigational agent outside of this protocol

	9. Known history of drug-specific hypersensitivity or anaphylaxis to rituximab or acalabrutinib (including active product or excipient components). 10. Active bleeding, history of bleeding diathesis (eg, hemophilia or von Willebrand disease) 11. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura) 12. The use of strong CYP3A inhibitors within 1 week or strong CYP3A inducers within 3 weeks of the first dose of study drug is prohibited 13. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug 14. Prothrombin time/INR or aPTT (in the absence of Lupus anticoagulant) > 2x ULN 15. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study 16. History of significant cerebrovascular disease or event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug 17. Breastfeeding or pregnant women 18. Concurrent participation in another therapeutic clinical trial 19. History of or ongoing confirmed progressive multifocal leukoencephalopathy (PML) 20. Significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification at Screening. Note: Subjects with controlled, asymptomatic atrial fibrillation are allowed to enroll on study

	21. Received a live virus vaccination within 28 days of first dose of study drug
Dose Regimen/Route of Administration:	Acalabrutinib is provided as hard gelatin capsules for oral administration approximately every 12 hours. Rituximab will be used as per clinical routine for IV infusion or as subcutaneous injection, and will not be provided within the trial.
Concomitant Medications:	<u>Prohibited Concomitant Therapy</u> Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone > 20 mg/day for longer than 2 weeks), experimental therapy, or radiotherapy for treating mantle cell lymphoma are prohibited. Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited. The concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 4) should be avoided when possible.