SYNOPSIS

Title	Venetoclax in combination with the BTK inhibitor Ibrutinib and Rituximab or conventional chemotherapy (Bendamustine) and Ibrutinib and Rituximab in patients with treatment naive Mantle Cell Lymphoma not eligible for high dose therapy
Short title	MCL-Elderly III
EudraCT	2020-002935-30
EU-CT	2022-501808-96-00
Sponsor trial code	20-01434
Indication	Mantle Cell Lymphoma
Phase	II
Experimental Treatment arms	Arm A (VR-I): Venetoclax, Rituximab, Ibrutinib Arm B (BR-I): Bendamustine, Rituximab, Ibrutinib
Study medication	Venetoclax, Ibrutinib
Primary objective and endpoint	To evaluate efficacy in both treatment arms: – Failure-Free Survival (FFS) at 30 months
Secondary objectives and endpoints	To evaluate efficacy, safety, tolerability, and quality of life in both treatment arms: – Failure-free survival (continuous observation) – Progression-free survival – Complete Remission rate (CR) and overall response rate (ORR: CR, PR) four weeks after the end of induction therapy – best response, time to best response, time to first response – overall survival – Overall survival of patients divided according to the geriatric categories and treatment received – Safety: adverse events, tolerability – Quality of life during induction and maintenance therapy (assessed using the EORTC QLQ-C30 and the EORTC QLQ-NHL-HG29) – Molecular remission after induction and conversion during maintenance (exploratory) – Immune reconstitution, e.g. persistence of anti-Covid19 immunity – safety and efficacy in different geriatric categories
Trial design	International, multicenter, open label, randomized phase II trial
Trial population	Key Inclusion Criteria: – Histologically confirmed diagnosis of MCL according to WHO classification – previously untreated stage II-IV (Ann Arbor) – ≥ 60 years and not suitable for autologous SCT – At least 1 measurable lesion; in case of bone marrow infiltration only, bone marrow aspiration and biopsy is mandatory for all staging evaluations. – ECOG performance status ≤ 2 The following laboratory values at screening (unless related to MCL): – Absolute neutrophil count (ANC) ≥ 1000 cells/µL – Platelets ≥75.000 cells/µL – Transaminases (AST and ALT) ≤3 x ULN – Total bilirubin ≤ 2 x ULN unless other reason known (Gilbert-Meulengracht-Syndrome)

	- Creatinine ≤ 2 mg/dL or calculated creatinine clearance ≥ 50 mL/min
	- Written informed consent form according to ICH/EU GCP and national regulations
	- Sexually active men and women of child-bearing potential must agree to use highly effective contraceptives
	
	Key exclusion criteria:
	- Major surgery within 4 weeks prior to randomization
	- Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon)
	- History of stroke or intracranial hemorrhage within 6 months prior to randomization
	- Treatment with strong or moderate CYP3A4/5 inhibitors/inducers within 7 days before first dose and during Venetoclax and Ibrutinib intake
	- Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of Ibrutinib capsules, or put the study outcomes at undue risk
	- Vaccinated with live, attenuated vaccines within 4 weeks prior to first dose
	- Known CNS involvement of MCL
	- Known bleeding disorder (e.g. von Willebrand disease; hemophilia)
	- Serious concomitant disease interfering with a regular therapy according to the study protocol:
	  - Cardiac (Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification or LVEF below LLN)
	  - Pulmonary (e.g. chronic lung disease with hypoxemia, e.g. DLCO ≤ 65% or FEV1 ≤ 65%)
	  - Endocrinological (e.g. severe, not sufficiently controlled diabetes mellitus)
	  - Patients with unresolved hepatitis B or C infection or known HIV positive infection (mandatory test)
	- Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer, Prostate cancer in remission with PSA within normal range or in situ uterine cervix cancer

Treatment schedule	**ARM A (VR-I):** Induction, cycle length 28 days: Venetoclax: Cycle 1: day 22-28 20 mg Cycle 2: day 1 - 7 50 mg day 8-14 100 mg day 15-21 200 mg day 22-28 400 mg Cycle 3-6: day 1-28 400 mg Rituximab: Cycle 1-6: day 1 375 mg/m^2 i.v. Ibrutinib: Cycle 1-6: day 1-28 560 mg Maintenance, cycle length 28 days:

	Venetoclax: Cycle 7–30: day 1-28 400 mg Rituximab: Cycle 7-30: day 1 of every second cycle 375 mg/m^2 i.v. Ibrutinib: Cycle 7-30: day 1-28 560 mg **ARM B (BR-I):** Induction, cycle length 28 days: Bendamustine: Cycle 1-6: day 1,2 90 mg/m^2 i.v. Rituximab: Cycle 1-6: day 0 or 1 375 mg/m^2 i.v. Ibrutinib: Cycle 1-6: day 1-28 560 mg Maintenance, cycle length 28 days: Rituximab: Cycle 7-30: day 1 of every second cycle 375 mg/m^2 i.v. Ibrutinib: Cycle 7-30: day 1-28 560 mg
Follow up	All subjects who enter the trial will continue to be followed every 6 months for disease progression, subsequent treatment, and survival until at least two years after last patient last treatment up to a maximum of 5 years (LPLT).
Number of subjects	It is planned to enroll 150 subjects
Randomization	A stratified central block randomization will be used for allocation of patients to both arms in a 1:1 ratio. Patients will be randomized until the final number is reached in each arm.
Number of sites	Approx. 40 trial sites are planned to participate in Germany and Italy