ABT-199 in combination with the BTK inhibitor i**B**rutinib and rituximab or conventional **C**hemotherapy (bendamustine) and ibrutinib and rituximabin patients with treatment naïve Mantle Cell Lymphoma not eligible for high dose therapy

A MULTICENTER RANDOMIZED PHASE II STUDY

OF THE *EUROPEAN MCL NETWORK*

Project Code:	ABC trial
Protocol Number	V-4.1
Date	26.09.2019
EUDRACT Number:	tbd
Included in clinicaltrials.gov database	Yes ☒ No ☐ NCT-No: tbd
Substance Identifier (IMP)	ABT-199 (Venetoclax), Ibrutinib
Therapeutic Area	Hematology/Oncology
Sponsor	Klinikum der Universität München, LMU on behalf of the *European MCL Network* Marchioninistrasse 15 81377 Munich, Germany
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1. Synopsis

Sponsor	Klinikum der Universität München, LMU on behalf of the *European MCL Network*
Protocol title	**A**BT-199 in combination with the BTK inhibitor i**B**rutinib (and rituximab) or conventional **C**hemotherapy (bendamustine) and ibrutinib (and rituximab) in mantle cell lymphoma
Trial design	multicenter phase II trial, two (independent) arms, open label, randomized of the *European MCL Network* The trial is an explorative ***Phase II*** trial from its design, looking at each group separately and all comparisons between groups will be descriptive and exploratory.
Investigational medicinal product	ABT-199 (Venetoclax), Ibrutinib
Number of subjects	2x 75 patients
Number of sites	40 centers in 3-5 countries of the *European MCL network:* Germany: GLSG, M. Dreyling, Munich Italy: FIL, N.N. other countries tbd
Scientific rationale	ABT-199 (Venetoclax) has achieved high response rates (75%) in relapsed MCL, but duration of remission after monotherapy seems to be limited (Gerecitano, ASH 2015, #254). Similarly, Ibrutinib is registered for relapsed MCL based on numerous phase II studies and a randomized phase III trial showing overall response rates of 70-80% with a progression-free survival of about 30-40% at 24 months (*Wang, NEJM 2013; Dreyling, Lancet 2016*). On the other hand, Bendamustine (in combination with Rituximab) has become standard of care in elderly MCL patients (*Rummel, Lancet Oncology 2013; Rummel, ASCO 2016*; *Dreyling, ESMO guidelines MCL 2017*). A current trial evaluates the combination of BR and ibrutinib which has the potential to become the new standard of care in first line therapy of elderly patients. The proposed phase II trial will explore the potentially optimal therapeutical approach of the pro-apoptotic ABT-199 (venetoclax) in combination with the BTK inhibitor ibrutinib and the anti CD20

	antibody rituximab or chemotherapy (bendamustine) in combination with ibrutinib and the anti CD20 antibody rituximab. If additional data are available supporting the superiority of obinutuzumab, this antibody will be applied instead in appropriate dose and schedule.
Primary study objectives	Failure-Free Survival (FFS) at 30 months
Secondary study objectives	- failure-free survival (continuous observation) - progression-free survival - response rates (CR, VGPR, PR, MR) and overall response rate (ORR) four weeks after the end of induction therapy - best response, time to best response, time to first response - molecular remission after induction and maintenance - overall survival - treatment associated adverse events - quality of life during induction and maintenance therapy
Exploratory study objectives	- molecular predictors of sensitivity (responders) and refractoriness (refractory/progressive disease)
Study Population -- Inclusion criteria	All patients must meet the following criteria: • Histologically confirmed diagnosis of MCL according to WHO classification • previously untreatedStage II-IV (Ann Arbor) • Age ≥ 60 years or ≥ 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/WHO 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 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 (eg, condoms, implants, injectables, combined oral contraceptives, intrauterine devices, sexual abstinence, or sterilized partner) while on study; this should be maintained for 90 days after the last dose of study drug.

Study Population -- Exclusion criteria	Any potential subject who meets any of the following criteria will be excluded from participating in the study. • Major surgery within 4 weeks prior to randomization. • Requires anticoagulation with warfarin or equivalent vitamin K antagonists (eg phenprocoumon). • History of stroke or intracranial hemorrhage within 6 months prior to randomization. • Requires treatment with strong CYP3A4/5 inhibitors. • 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 randomization. • Known CNS involvement of MCL • Clinically significant hypersensitivity (eg, anaphylactic or anaphylactoid reactions to the compound of ibrutinib itself or to the excipients in its formulation) • Known anti-murine antibody (HAMA) reactivity or known hypersensitivity to murine antibodies • 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) – Endocrinological (e.g. severe, not sufficiently controlled diabetes mellitus) Patients with unresolved hepatitis B or C infection or known HIV positive infection (mandatory test) • Prior organ, bone marrow or peripheral blood stem cell transplantation • Concomitant or previous malignancies within the last 3 years other than basal cell skin cancer or in situ uterine cervix cancer • Pregnancy or lactation • Any psychological, familiar, sociological, or geographical condition potentially hampering compliance with the study protocol and follow up schedule • Subjects not able to give consent • Subjects without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial • Participation in another clinical (AMG) trial within 30 days before randomization in this study.

Treatment schedule	*Figure 1: Flow sheet* *ARM A (AIR):* *Venetoclax:* Cycle 1: day 22-28 20 mg (2 tablets at 10 mg) Cycle 2: day 1-7 50 mg (1 tablet at 50 mg) day 8-14 100 mg (1 tablet at 100 mg) day 15-21 200 mg (2 tablets at 100 mg) day 22-28 400 mg (4 tablets at 100 mg) Cycle 3-30: day 1-28 400 mg (4 tablets at 100 mg) *Ibrutinib:* Cycle 1-30: day 1-28 560 mg (4 tablets at 120 mg) *Rituximab:* Cycle 1-6: day 1 375 mg/m2 i.v. maintenance day 1 375 mg/m2 i.v. (every 2 months) *ARM B (BR-I):* *Bendamustine* Cycle 1-6: day 1,2 90 mg/m2 i.v. *Rituximab:* Cycle 1-6: day 1 375 mg/m2 i.v. maintenance day 1 375 mg/m2 i.v. (every 2 months) *Ibrutinib:* Cycle 1-30: day 1-28 560 mg (4 tablets at 120 mg) ***Follow-up Phase*** All subjects who enter the trial will continue to be followed every 3 months for disease progression, subsequent treatment, and survival for two years after completion/ discontinuation of induction treatment (month 6). Subsequently, patients will be monitored every 6 months for three additional years. ***Data and Safety Monitoring Committee*** A Data and Safety Monitoring Committee (DSMC) will be installed and composed of 3 members, including a statistician, who are not involved in the execution of the trial.

	Reference Pathology Archival lymph node or bone marrow biopsy specimen obtained preferable at last relapse or (in refractory cases) at the time of initial diagnosis with representative stained slides, must be submitted to the national reference pathology as part of the baseline screening (preferentially whole tumor blocks, and both unstained and HE stained slides). A major focus of the study will be the identification of the underlying molecular mechanisms resulting in sensitivity or refractoriness. ***Minimal residual disease*** For exploratory analysis of MRD peripheral blood and bone marrow (if clinically indicated) will be analysed prior to treatment, after completion of induction and end of maintenance.
	The trial is an explorative ***Phase II*** trial from its design, looking at each group separately and all comparisons between groups will be descriptive and exploratory. **Sample Size:** The goal of this study is to explore the efficacy of a chemotherapy - free combination of ABT-199/ibrutinib (and rituximab) or a combined approach (bendamustine-rituximab) and ibrutinib in previously untreated MCL, aiming to significantly improve tolerability with at least comparable failure-free survival. These data may be potentially extended to a formal phase III study comparing both combinations. The rate of first-line patients achieving a failure-free survival of more than 30 months after start of therapy will serve as early readout for long term efficacy and will be the primary endpoint of this trial. We aim to assess the estimate for 30-months FFS in both arms with prespecified precision, expressed as the half-width of the two-sided 95% confidence interval. Irrespective of the true, but unknown value for 30-months FFS, the confidence interval should be assessed with a precision of +/- 12.5%. Using the exact Pearson-Clopper values a sample size of n=67 for each study arm is needed. Assuming a drop-out rate of about 10%, 75 patients in each group are needed, in total 150 patients. FFS will be continuously monitored during the study. **Randomization:** A stratified central block randomization will be used for allocation of patients to both arms, using the additional rituximab treatment (rituximab-sensitive cases only) as strata. Patients will be randomized until the final number is reached in each arm.

	Analysis of Primary Endpoint: The primary parameter FFS will be evaluated in a full intention to treat way, so that only withdrawal of informed consent or lack of staging result at 30 months will make observations not evaluable for the primary endpoint. It is expected, that the rate of dropouts is smaller than 10%. For the primary endpoint the 95% exact confidence interval will be estimated using the Pearson-Clopper values. As sensitivity analysis, Kaplan-Meier estimates with log-log-confidence intervals will be calculated using censored observations as far as possible. Subgroup analysis for Rituximab-use will be done by descriptive methods. Additionally, a descriptive and exploratory comparison between both groups of the 30 months PFS rate will be carried out using the Fishers exact test or logrank test as appropriate. For the group difference of the 30 months PFS rate, 95% confidence intervals will be calculated for each comparison. **Analysis of Secondary Endpoints:** All secondary endpoints will be evaluated in a descriptive way with 95% confidence intervals provided for numeric estimates. For time event data Kaplan-Meyer-Estimates will be provided with 95%-CI for one, two, and three years.
Duration of recruitment	Approximately 3 years
Study Duration	up to 5.5 years
First patient in	2020; Q2
Last patient out	2025; Q4