1.2 Study Synopsis

Clinical study title	A Prospective multicenter Phase 2 Study of the Chemotherapy-Free Combination of the Intravenous Phosphatidylinositol-3-Kinase (PI3K) Inhibitor Copanlisib in Combination with Obinutuzumab in Patients with Previously Untreated Follicular Lymphoma (FL) and a High Tumor Burden
Phase of study	II
Short title	Copanlisib in Combination with Obinutuzumab in Patients with Previously Untreated Follicular Lymphoma (FL)
Sponsor Code	ALTERNATIVE-C
EudraCT No.	2018-004038-13
Investigational medicinal product, dose and mode of application	Trade Name: ALIQOPA™ Substance: Copanlisib Manufacturer: Bayer AG Dose: 60 mg Mode of Application: intravenous Duration of Treatment: 30 months
Investigational medicinal product, dose and mode of application	Trade Name: GAZYVARO® Substance: Obinutuzumab Manufacturer: Roche AG Dose: 1000 mg Mode of Application: intravenous Duration of Treatment: 30 months
Study treatment plan	**Induction therapy** will comprise 6 cycles of copanlisib plus obinutuzumab: Copanlisib will be administered by intravenous infusion at a dose of 60 mg on day 1, 8, 15 of cycles 1-6 to be given every 28 days. Copanlisib must be administered before obinutuzumab application. Obinutuzumab will be applied at a dose of 1000 mg by intravenous infusion on days 1, 8, 15 of cycle 1 and on day 1 of cycles 2-6 to be given every 28 days. **Consolidation therapy** will comprise another 24 weeks (6 months) of copanlisib plus obinutuzumab in patients with clinical remission 28 days after the last induction cycle: Copanlisib will be administered by intravenous infusion at a dose of 60 mg on days 1 and 15 of cycles 7-12 to be given every 28 days. Copanlisib must be administered before obinutuzumab application. Obinutuzumab will be applied at a dose of 1000 mg by intravenous infusion every 8 weeks.

	Maintenance therapy will comprise another 72 weeks (approx. 18 months) of copanlisib plus obinutuzumab in patients with clinical remission 28 days after the last consolidation cycle: Copanlisib is applied at a dose of 60 mg every 8 weeks. Obinutuzumab will be applied at a dose of 1000 mg by intravenous infusion every 8 weeks. The total duration of copanlisib plus obinutuzumab therapy will therefore be 120 weeks (approx. 30 months (39 doses of copanlisib + 20 doses of obinutuzumab).
Study population (or indication)	Patients ≥ 18 years of age with histologically confirmed follicular lymphoma grade 1, 2 or 3A with Ann Arbor Stage III/IV or stage II not suitable for radiotherapy and in need of therapy. See Inclusion/Exclusion criteria below.
Study design	Prospective, multicenter phase-II-study
Study objectives	The primary objective of this study is to evaluate the efficacy of the chemotherapy-free combination of copanlisib and obinutuzumab in patients with previously untreated follicular lymphoma (FL) and a high tumor burden. The secondary objectives are to evaluate the new combination in terms of secondary efficacy endpoints, treatment compliance, safety and patient-reported symptoms.
Study endpoints	**Primary endpoint:** • One-year progression-free survival (PFS) probability from study registration. **Secondary endpoints:** • Complete remission (CR) rates and overall response (CR or partial remission, PR) rates at end of induction (month 6), at end of consolidation (month 12), and at end of maintenance (month 30) • Progression free survival from registration (continuous observation) • Duration of response from end of induction to progression or death • Cumulative incidence of progression from registration • Failure-free survival from start of therapy (event defined by failure to achieve a CR/PR after 6 months or progression after CR or PR or death from any cause) • Time to next anti-lymphoma therapy and time to next chemotherapy based treatment from start of first-line therapy • Overall survival from registration • Treatment associated adverse events

	• Percentage of MRD-negative patients at midterm induction, at end of induction therapy (month 6), at end of consolidation therapy (month 12), and at end maintenance therapy (month 30) • Duration of molecular remission for MRD negative patients from end of induction therapy • Cumulative incidence of secondary transformations to aggressive lymphoma • Cumulative incidence of secondary malignancies • Percentage of patients with compliance to therapy after 6, 12, and 30 months • Frequency of patient-reported lymphoma symptoms and concerns (FACT-Lym)
Subject number	A total number of 102 subjects will be enrolled.
Inclusion criteria	Subjects will only be included in the study, if they meet all of the following criteria: • Histologically confirmed follicular lymphoma grade 1, 2 or 3A with a biopsy performed within 12 months before study entry and with material available for central review and complementary scientific analyses • Ann Arbor stage III/IV, or stage II not suitable for radiotherapy, or stage II bulky disease • Age ≥ 18 years • No prior lymphoma therapy • Need for start of therapy as defined by at least one of the following criteria: - bulky disease at study entry according to the GELF criteria (nodal or extranodal mass > 7 cm in its greatest diameter) - B symptoms (fever, drenching night sweats, or unintentional weight loss of > 10% of normal body weight over a period of 6 months or less) - hematopoietic insufficiency (granulocytopenia < 1500/µl, Hb < 10 g/dl, thrombocytopenia < 100000/µl) - compressive syndrome or high risk for compression syndrome - pleural/peritoneal effusion - symptomatic extranodal manifestations • At least one bi-dimensionally measurable lesion (> 2 cm in its largest dimension by CT scan or MRI) • Performance status ≤ 2 on the ECOG scale

	• Adequate hematologic function (unless abnormalities are related to NHL), defined as follows: - Hemoglobin ≥ 9.0 g/dL - Absolute neutrophil count ≥ 1500/µl - Platelet count ≥ 75000/µl • Women are not breast feeding, are using highly effective contraception (see section 11.4.1), are not pregnant, and agree not to become pregnant during study treatment and for 18 months after last application of Obinutuzumab and for one month after last application of Copanlisib (pregnancy testing is mandatory for premenopausal women). • Men agree not to father a child during study treatment and for 18 months after last application of Obinutuzumab and for one month after last application of Copanlisib. • Written informed consent
Exclusion criteria	Subjects will not be included in the study if any of the following criteria apply: • • Transformation to high-grade lymphoma (secondary to "low grade" FL) • Grade 3B follicular lymphoma • Presence or history of CNS disease (either CNS lymphoma or leptomeningeal lymphoma) • Known hypersensitivity to any of the study drugs • Known sensitivity to murine products • Patients with HbA1c > 8.5 % at Screening • Uncontrolled arterial hypertension despite optimal medical management (per investigator' s assessment) • Regular use of corticosteroids during the last 4 weeks, unless administered at a dose equivalent to < 20 mg/day prednisone or administered as prephase treatment according to study protocol (see section 7.2 of study protocol) • Concomitant use of strong CYP3A4 inhibitors and/or inducers • Prior or concomitant malignancies except: - non-melanoma skin cancer or adequately treated in carcinoma in situ of the cervix - other malignant diseases not specified above which have been curatively treated by surgery alone and from which subject is disease-free for ≥ 5 years without further treatment • Serious disease interfering with a regular therapy according to the study protocol: - 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 - pulmonary (e.g. chronic lung disease with hypoxemia) - endocrine (e.g. severe, not sufficiently controlled diabetes mellitus) - renal insufficiency (unless caused by the lymphoma): creatinine > 2x normal value and/or creatinine clearance < 50 ml/min) - impairment of liver function (unless caused by the lymphoma): transaminases > 3x normal or bilirubin > 2.0 mg/dl (unless caused by known Morbus Meulengracht [Gilbert-Meulengracht-Syndrome]) • Positive test results for chronic HBV infection (defined as positive HBsAg serology) Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible. • Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing) Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA. • Clinically significant history of liver disease, including viral or other hepatitis, or cirrhosis • Known history of HIV seropositive status • Patients with a history of confirmed PML • Vaccination with a live vaccine within 28 days prior to registration • Recent major surgery (within 4 weeks prior to the start of Cycle 1) • History of stroke or intracranial hemorrhage within 6 months prior to registration • Serious underlying medical conditions, which could impair the ability of the patient to undergo the treatment offered in the study (e.g. ongoing infection, gastric ulcers, active autoimmune disease) • Treatment within another clinical study within 30 days prior to study entry • Prior organ, bone marrow, or peripheral blood stem cell transplantation • Known or persistent abuse of medication, drugs, or alcohol • Any other co-existing medical or psychological condition that will preclude participation in the study or compromise ability to give informed consent
Efficacy evaluations	Assessment of tumor response and progression will be conducted in accordance with the 2014 Lugano Classification (without using a

	PET-CT). Efficacy evaluations include physical examination including lymphoma B symptoms, computed tomography scans, magnetic resonance imaging, if applicable, bone marrow aspirate and biopsy, or other procedures as necessary. Efficacy evaluations will be performed after 6 cycles of induction treatment, and every 6 months after induction until clinical progression. Subjects who discontinue treatment prior to disease progression will have regularly scheduled disease evaluations until disease progression, death, or study end, whichever occurs first. For all subjects, survival and subsequent antineoplastic therapy data will be collected until lost to follow-up, withdrawal of consent, or study end. In addition MRD is assessed by PCR on peripheral blood samples collected before the start of therapy and at months 3, 6 and 12, respectively. Subsequently, samples for MRD analyses will be collected every 6 months until clinical progression of the disease or for a maximum total of 5,5 years for later analysis.
Investigational study sites	The study will be conducted in approximately 40 sites in Germany, which must meet the structural and personnel requirements for performing the planned regular study-related investigations. All investigators agree to supervise the conduct of this study in their affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the EU directive Good Clinical Practice (2001-20-EG), and local regulations governing the conduct of clinical studies.
Statistical rationale	The study will enroll a maximum of 102 subjects based on the following considerations: In advanced stage follicular lymphoma (FL) long lasting periods of progression-free survival of about 10 years are currently achieved by standard immuno-chemotherapy including two years of maintenance. Still, FL remains an incurable disease, and relapses constantly occur. New therapies must therefore not only aim at a further enhancement of anti-lymphoma activity but also at a reduction of treatment associated side effects and long term toxicities such as secondary malignancies. Copanlisib plus obinutuzumab may provide a highly attractive chemotherapy-free alternative to standard immuno-chemotherapy by combining a high anti-lymphoma activity with a convenient form of application and by avoiding the objective and subjective disadvantages of standard cytotoxic chemotherapy. These prerequisites provide the basis for the statistical rationale of the proposed study. It comprises the evaluation of the efficacy and tolerability of the new copanlisib/obinutuzumab combination in comparison with the estimates from the preceding R-CHOP study of the GLSG. In addition to progression-free survival as primary

	endpoint serial measurements of MRD will be performed by PCR during induction and consolidation to not only evaluate the anti-lymphoma efficacy of the new chemotherapy-free copanlisib/obinutuzumab combination but also to generate information on the duration and effect of maintenance therapy. Primary endpoint The rate of patients achieving a progression free survival of more than one year after registration (one-year PFS rate) will serve as early readout for efficacy and will be the primary endpoint of this study. Chemotherapy without antibody-therapy but with post remission therapy (IFN or high dose therapy with stem cell support) did archive a one-year PFS of 84.5 % in the GLSG study comparing CHOP with R-CHOP. For the R-CHOP therapy the one-year PFS was 92.6%, while progression free survival after three years was 73.6%. Using obinutuzumab in combination with chemotherapy and maintenance, at least a progression free survival of 77.4% after three years is expected (hazard ratio 0.74). Using the proportional hazard assumption, the one-year PFS rate for an obinutuzumab combination with chemotherapy should be about 94.4%. According to the data for chemotherapy without antibodies, the one-year PFS rate must be better than 85% and the probability to accept a chemotherapy free combination with a real one-year PFS rate ≤ 85% should be safely controlled and smaller than 5%. If a combination has a one year PFS of about 95%, it will be a good candidate for challenging immuno-chemotherapy and the probability for accepting this combination for further evaluation should be about 95%. So the decision about the new combination will be based on a binomial test of the form HA: { one-year PFS rate > 85%} vs. H0: { one-year PFS rate ≤ 85%} with a working significance level α=0.05 and a power of 95% for a reference improvement of 10% to 95%. For these parameters the observation of 93 full evaluable patients will be necessary. For a smaller improvement of 9% (8%) the test will then still provide a power of about 90% (80%). The primary parameter PFS rate will be evaluated in a full intention to treat way, so that only patients without observed progression or death during the first year but with missing staging result one year after registration will be excluded for the evaluation of the primary endpoint. It is expected, that the rate of non-evaluable patients is smaller than 9%. As secondary sensitivity analysis, we will evaluate the 1-year PFS rate counting patients non-evaluable for the primary endpoint as PFS failures. According to these specifications, the study will enroll a maximum of 102 subjects. PFS will be monitored during the study and if more than 8 failures for PFS are observed

	during the first year after registration, recruitment will be stopped for futility. Progression-free survival (PFS) rate is chosen as primary endpoint since it represents beside overall survival the most relevant parameter for patients. PFS is defined as the time from registration to lymphoma progression or death from any cause. <u>Safety analysis:</u> Safety evaluations include: adverse event monitoring, physical examinations, evaluation of changes to concomitant medications, and clinical laboratory parameters. All adverse events that occur between the date of subject registration through 28 days after subjects have completed study treatment will be collected. Infections and secondary malignancies will be reported during the whole duration of the study. The severity of adverse events will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0. Serious adverse events will be reported according to the GCP regulations.
Time schedule	<u>Study duration:</u> With an expected recruitment of about 100 patients per year, recruitment for the copanlisib/obinutuzumab combination should be finished within one year. After the end of induction which should be finished after six months, a consolidation phase of 6 months, a maintenance phase of 18 months and a minimum follow up phase of 2 years follows. So the study is expected to be closed 5,5 years after start of recruitment. Since recruitment was slower than expected due to SARS-CoV-2 pandemia, a prolongiation of the study may become necessary and will be fixed in a further amendment.
Reports	No interim report for efficacy will be provided before decision of the statistical test. The evaluation of the primary endpoint will be done one year after the end of recruitment, when complete data for all patients for the first year are evaluable. After this evaluation, yearly follow-up reports are provided until the study is closed and the final report is created.
Complementary Research	MRD monitoring will be regularly performed on peripheral blood samples collected before the start of therapy and at months 3, 6, and 12 respectively. Subsequently, samples for MRD analyses will be collected every 6 months until clinical progression of the disease or for a maximum total of 5,5 years for later analysis. At the same timepoints peripheral blood plasma samples to isolation of ctDNA will be collected. A central pathology review process will be part of this study in the way that tumor paraffin embedded blocks from formalin fixed samples that were used for diagnoses will be shipped for central

	pathological review and DNA/RNA extraction (mutation profile and NanoString immune profiling).