Expansion (Part 2)
Patients will receive BYON4228 at the RDE(s) in combination with rituximab in the following 2 patient cohorts:

A. Histologically confirmed aggressive B-cell NHL (e.g., DLBCL, MCL) expressing CD20 by IHC or flow cytometry, R/R to at least 1 prior line of therapy.
B. Histologically confirmed indolent B-cell NHL (e.g., marginal zone, follicular lymphoma (Grade 1-3a)) expressing CD20 by IHC or flow cytometry, R/R to at least 2 prior lines of therapy.

This part of the study will consist of 2 cohorts. Up to 14 eligible patients as per inclusion and exclusion criteria will be enrolled in each cohort. If there are more than 2 responders in the 14 patients, a maximum of 10 additional patients may be enrolled for a total of 24 patients per cohort.

8. Trial population

All patients must provide their written informed consent before any protocol specific procedures, including screening procedures, are performed. Patients should comply with all inclusion and exclusion criteria as described below.

8.1. Eligibility criteria

When evaluating a patient for participation into the study the investigator should first perform an evaluation if the patient is suitable for rituximab treatment, all clinical considerations, including specific restrictions/contraindications as per SmPC for rituximab should be taken into account. Only after it is concluded that a patient is suitable to receive rituximab treatment, the patient can be considered for the study as per inclusion/exclusion criteria.

8.2. Inclusion criteria

1. Male or female, age ≥ 18 years at the time of signing informed consent;
2. Patient with:
   a. Part 1 only: (Aggressive or indolent) B-cell NHL expressing CD20 by immunohistochemistry (IHC) or flow cytometry, R/R to at least 2 prior lines of therapy;
   b. Part 2 cohort A only: Histologically confirmed agressive B-cell NHL (e.g., DLBCL, MCL) expressing CD20 by IHC or flow cytometry, R/R to at least 1 prior line of therapy;
   c. Part 2 cohort B only: Histologically confirmed indolent B-cell NHL (e.g., marginal zone, follicular lymphoma (Grade 1-3a)) expressing CD20 by IHC or flow cytometry, R/R to at least 2 prior linesof therapy;

   For both parts: autologous hematopoietic stem cell transplantation (HSCT) and autologous CAR-T cell therapy (if more than 3 months prior to start IMP), and allogeneic HSCT (if more than 6 months prior to start IMP) are allowed as prior lines.
3. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1;
4. For Part 2 only: Disease that is measurable or assessable for response per Lugano Classification for lymphomas;
5. Laboratory measurements, blood counts (GF support and blood transfusions are not allowed 2 weeks prior to this assessment):
   a. Hemoglobin ≥ 8.5 g/dL (≥ 5.28 mmol/L);
   b. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L;
   c. Platelet counts ≥ 50×10^9/L; If bone marrow involvement: ≥ 25×10^9/L;

6. Laboratory measurements, hepatic function:
   a. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) < 5 × upper limit of normal(ULN);
   b. Total bilirubin ≤ 1.5 × ULN or 3.0 × ULN and primarily unconjugated if patient has a documented history of Gilbert's syndrome or a genetic equivalent;
7. Laboratory measurements, renal function: Serum creatinine ≤ 1.5 × ULN or calculated glomerular filtration rate (GFR) >30 mL/min/1.73 m^2 (calculated with CKD-EPI formula)
8. Females of childbearing potential must be willing to use a highly effective method of contraception during the study and for 12 months after the last dose of rituximab or for 6 months after the last dose of BYON4228, whichever takes longer;

8.3. Exclusion Criteria

1. Having been treated with
   a. CD47 or SIRPα targeting agents at any time;
   b. Other anticancer therapy including investigational agents within 2 weeks prior to start BYON4228 treatment or within 4 times the elimination half-life (up to a maximum of 4 weeks) whichever is longer. Note: treatment with hormonal therapy with LHRH agonists for localized prostate cancer, and treatment with bisphosphonates and RANKL inhibitors are not criteria for exclusion;
   c. Radiotherapy within 1 week prior to start of BYON4228;
   d. Autologous HSCT or CAR-T cell therapy within 3 months prior to start IMP, or allogeneic HSCT within 6 months prior to start IMP.

   In addition, the patient must have sufficiently recovered from any treatment-related toxicities to CTCAE Grade ≤ 1 or baseline, except for toxicities not considered a safety risk for the patient at the investigator's discretion;
2. Any contraindication to rituximab treatment;
3. History of hypersensitivity or allergic reaction to any of the excipients of BYON4228 or rituximab which led to permanent discontinuation of the treatment;
4. Currently diagnosed or suspected CNS involvement;
5. Burkitt's lymphoma;
6. Known active or chronic (DNA or RNA positive) hepatitis B, C or E infection or human immunodeficiency virus (HIV);
7. Red blood cell (RBC) transfusion dependence, defined as requiring more than 2 units of RBC transfusions during the 4-week period prior to screening;
8. Patients with active graft versus host disease (GVHD) or ongoing immunosuppression for GVHD;
9. History of autoimmune hemolytic anemia or autoimmune thrombocytopenia that in the investigator's opinion is likely to jeopardize patient safety;
10. History of autoimmune disorders (including but not limited to: Crohn's disease, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, Grave's disease) or other conditions that compromise or impair the immune system (except for hypogammaglobulinemia) and that in the investigator's opinion is likely to jeopardize patient safety;
11. Second malignancy, other than the one treated in this trial, in the last 3 years before signing ICF. Except, if appropriately treated: basal cell or localized squamous skin carcinomas, localized prostatecancer, localized cervical cancer or other indolent malignancy;

12. History (within 6 months prior to start of BYON4228 treatment) or presence of clinically significant cardiovascular disease such as unstable angina, congestive heart failure, myocardial infarction, uncontrolled hypertension, or cardiac arrhythmia requiring medication. Presence of atrial fibrillation is allowed if in the investigator's opinion is not likely to jeopardize patient safety;
13. Severe active infection or other severe uncontrolled systemic disease (e.g., advanced renal disease, pulmonary, uncontrolled diabetes mellitus, severely immunocompromised state, or metabolic disease) at screening;
14. Major surgery within 4 weeks prior to start of BYON4228 treatment;
15. Pregnancy or active breastfeeding;
16. Other conditions that in the investigator's opinion is likely to jeopardize patient safety or interfere with the patient's ability to comply with trial requirements.

8.4. Screen failures

Patients who signed the informed consent form (ICF) but failed to meet the inclusion and/or exclusion criteria are defined as screen failures.

Individual screening assessments may be repeated once to exclude an unexpected error or exceptional variability. It is not allowed to re-screen more often to preclude testing into compliance, except for hemoglobin as indicated in exclusion criterion 6. In exceptional cases it might be allowed to prolong the screening period of 28 days, after consultation and approval by the Sponsor. Some safety assessments may have to be repeated in such situation.

For screen failures, a limited number of CRFs will have to be completed as documented in the CRF completion guidelines.

9. Trial medication and dosing instructions

In this trial BYON4228 is the investigational medicinal product (IMP) and rituximab is used as background IMP.

Detailed instructions for BYON4228 preparation and handling are provided in the Pharmacy Manual. For rituximab the current European SmPC includes the instructions.

BYON4228 will be administered every 4 weeks (4-weekly dosing cohorts). Two-weekly dosing cohorts (and/or other dosing frequencies) may also be evaluated, depending on results collected. Rituximab will be administered first cycle weekly (for CLL/SLL: first cycle 1 dose), thereafter every 4 weeks for a total of 6 cycles. In Part 1 the first cycle will be BYON4228 alone, from the second cycle onwards dosing with BYON4228 and rituximab will be combined for 6 cycles. Patients will be required to stay overnight after the first infusion of BYON4228 alone and after the first infusion of BYON4228 and rituximab combined for safety monitoring. In Part 2 BYON4228 dosing will be combined with rituximab from the first cycle onwards for 6 cycles. Drug administration schedules are summarized in **Table 1**. Dosing should be discontinued upon disease progression or unacceptable toxicity. In responders, dosing may be continued beyond 6 cycles of combination therapy, if in best interest for the patient at the investigator's discretion, and upon Sponsor and medical monitor approval.