CLINICAL PROTOCOL PSB202-01

A Phase 1a/1b Study of PSB202 in Patients with Previously Treated, Relapsed, Indolent B-Cell Malignancies

Investigational Product:	PSB202
Protocol Number:	PSB202-01
Development Phase:	1
IND #:	154242
Sponsor (US – IND):	Qilu Puget Sound Biotherapeutics, Corp. (dba Sound Biologics); Bothell, WA
Sponsor (China – C-IND)	Qilu Pharmaceuticals Co. Ltd, Jinan, China
Initial Version	21 January 2021
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SPONSOR'S APPROVAL

Protocol Title:	A Phase 1a/1b Study of PSB202 in patients with previously treated-, relapsed-, indolent B-Cell malignancies
Protocol Number:	PSB202-01
Initial Version 1.0	14 January 2021
Version 2.0	20 March 2023

The current version of the protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature below. The study will be conducted in compliance with this Clinical Study Protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonisation (ICH) E6 (R2), and all applicable local and national regulatory requirements.

Sponsor:

Qilu Pharmaceuticals Co. Ltd, Jinan, China
Xiaoyan Kang, MD, PhD
Chief Medical Officer

Signature: Date:

SYNOPSIS

TITLE:

A Phase 1a/1b Study of PSB202 in patients with previously treated-, relapsed-, indolent B-Cell malignancies

PROTOCOL NUMBER:

PSB202-01

STUDY SITES:

Approximately 10-16 institutions are planned for participation in this study: 7-10 in Phase 1a (dose escalation) and 10-16 in Phase 1b (Cohort expansion). Phase 1a institutions who enroll at least 2 patients into Phase 1a will be invited to continue as 1b sites, even as additional 1b sites will be added at that time.

PHASE:

1a/1b (Two-part study)

OBJECTIVES:

Primary Objective (Phase 1a – Dose Escalation):

To determine the maximum tolerated dose (MTD)/recommended Phase 1b dose (RPIbD) of PSB202 for Phase 1b and further trials in previously treated indolent B-cell malignancies – specifically indolent/ B-cell non-Hodgkin lymphomas (NHL), chronic lymphocytic Leukemia / small lymphocytic lymphoma (CLL/SLL) and Waldenström Macroglobulemia (WM).

Secondary Objectives (Phase 1a – Dose Escalation):

- To determine the safety profile and tolerability of PSB202 including acute and chronic toxicities, and possible treatment-emergent appearance of anti-drug antibodies (ADA).
- To characterize the pharmacokinetics (PK) and pharmacodynamic (PD) properties of PSB202.
- To assess the preliminary anti-tumor activity of PSB202 based on overall response rate (ORR) according to International Workshop Guidelines for CLL/SLL (IWCLL 2018, (Hallek, Cheson et al. 2018)) and Waldenström macroglubulemia WM (IWWM8, Appendix D (Leblond, Kastritis et al. 2016)), Marginal Zone Lymphoma (MZL) and other indolent NHL (Lugano 2014, Appendix E (Cheson, Fisher et al. 2014)), or other criteria as appropriate to tumor type, as assessed by the Investigator.

Primary Objective (Phase 1b – Dose Expansion):

- To assess the anti-tumor activity of PSB202 based on ORR (Investigator).

Secondary Objectives (Phase 1b – Dose Expansion):

To assess, for each Phase 1b cohort, the preliminary anti-tumor activity of PSB202 by determining:

ORR as assessed by the Central Review

Best overall response (BOR) as assessed by the Investigator

Duration of response (DOR) as assessed by the Investigator

Progression free survival (PFS) as assessed by the Investigator

To determine the safety profile and tolerability of PSB202.

To characterize the PK/PD properties to produce evidence of biological impact for PSB202.

Exploratory Objectives (Phase 1a):

To determine the relationship between PK and drug effects, including efficacy and safety.

Exploratory Objectives (Phase 1a and Phase 1b):

In CLL/SLL patients meeting clinical response criteria for complete response (CR), to evaluate minimal residual disease (MRD), assessed in the peripheral blood and/or bone marrow, by molecular assays including next-generation sequencing (NGS), allele-specific oligonucleotide polymerase chain reaction (PCR) and/or flow cytometry, in patients meeting response criteria for complete response (CR).

In follicular lymphoma (FL) patients: to characterize reversion of peripheral blood *BCL-2* rearrangement.

STUDY DESIGN:

This is an open-label, multi-center Phase 1a/1b study of intravenous PSB202 in patients with indolent B cell NHL (including CLL/SLL, FL1-3a, MZL, WM and MCL indolent subtype) who have failed or are intolerant to standard of care therapy. This study includes 2 parts: Phase 1a (dose escalation) and Phase 1b (dose expansion). In phase 1a, patients will be enrolled using a modified 3+3 design – modified by use of accelerated titration in the three lowest- and possibly sub-therapeutic dose levels. The starting dose of PSB202 is 12 mg in 3 loading doses by *i.v.* infusion on D1, D8 and D15 of Cycle 1, followed by 12 mg *i.v.* on D1 of subsequent cycles.

The planned Phase 1a dose levels are in provided **Table 1**.

The Sponsor aims to achieve diversity among various indolent B-cell malignancies in

Phase 1a (escalation) to avoid that the enrolled trial population is dominated by CLL/SLL, thus yielding insufficient safety data on NHL. Hence, other than as backfill described below, the number of CLL/SLL patients will be capped at no more than 2 DLT-evaluable patients per 3-patient dose-escalation cohort (or 3 DLT-evaluable *maximum* share if cohort is expanded to 6 patients).

The determination of the PSB202 dose for the Phase 1b portion of the study will take into account the entirety of PK, PD, efficacy and safety data. Once the MTD and/or recommended Phase 1b dose is identified, patients will be enrolled to one of three Phase 1b dose expansion cohorts depending on tumor histology. If merited by the emerging Phase 1a data, a separate Phase 2 protocol may be developed for CLL.

A recommended Phase 1b/Phase 2 dose will be confirmed independently for CLL- versus non-CLL patients. Prior to opening Phase 1b expansion cohorts and/or Phase 2 studies, the Phase 1a dose level that suggests the MTD or recommended Phase 1b dose may be expanded with additional patients until a minimum of 6 patients are have been treated with the disease histology considered for 1b Expansion (CLL versus non-CLL). The opening of CLL- and non-CLL expansion cohorts may proceed along independent timelines once a recommended Ph1b dose with a DLT-rate < 33% is confirmed, guided by safety /DLT data from at least 6 patients of corresponding histology. Dose de-escalation is possible if one disease histology exhibits a markedly different safety profile versus another histology. This approach allows for the possibility that a different MTD and hence a different Phase 2 or Phase 1b dose is characterized and selected for CLL- versus non-CLL expansion cohorts.

Phase 1a Design:

Phase 1a will enroll patients with histologically confirmed relapsed WM, indolent NHL, or CLL/SLL who have failed or are intolerant to standard of care. In the opinion of the investigator, patients must have exhausted available standard-of-care options and require systemic therapy based on disease-specific criteria (see Appendices C, D, E).

Previous studies with CD20+ targeted agents indicate that significant (e.g., 90% or greater) CD20 target engagement in patients is required for clinical efficacy (Byrd, Furman et al. 2013, Woyach, Furman et al. 2014, Tam, Grigg et al. 2015). Hence three study drug administrations are provided in Cycle 1(C1, Day 1, Day 8 and Day 15). The starting dose of PSB202 is 12 mg *i.v.* infused over four hours. Absent Grade 2 or worse infusion reactions (IRR) during Cycle 1, the infusion speed may be increased step-wise at subsequent infusions to infusion of the full experimental dose over two hours. Dosing is not adjusted for weight or body surface area. The DLT period will be 28 days, commencing with the first dose of PSB202. Cycle length will be 21 days. Hence the DLT period includes the full first cycle and up to the first 7 days of follow-up of the second cycle if the C2, D1 dose is given per the protocol-directed schedule.

Dose escalation will follow an accelerated titration design with a single patient in the first

three dose levels (12 mg, 36 mg and 100 mg), progressing with the standard 3 + 3 design at all higher dose levels. In the single-patient cohorts, the occurrence of a single ≥ Grade 2 or higher AE during the 28-day DLT observation period, that cannot be reasonably attributed to the patient's underlying disease, other medical conditions or concomitant medications, will result in a switch to a 3+3 dose escalation design for this and subsequent dose levels. It is hoped that an accelerated titration design will minimize the number of patients exposed to subtherapeutic doses of PSB202 and hasten the identification of a safe and therapeutic dose.

Dose escalations will be ~3 times the previous dose level for the first 3 dose escalations. After the third dose increase, a modified Fibonacci dose escalation will be used to guide subsequent increases, with planned increments of ~100%, ~67%, ~50%, and then ~33% for further dose escalations. In addition, the Safety review committee (SRC) may modify the actual dose escalated to, suggest an intermediate level not specified in Table 1, or the dosing schedule may be changed, upon review of available PK, safety and efficacy data. Individual dose escalation of patients enrolled in lower-dose cohorts to the next higher dose-cohort (i.e. intra-patient dose escalation) may be offered once the next higher dose cohort has been cleared as safe by the SRC. Planned dose levels for PSB202 are shown in **Table 1**.

Table 1 Planned Dose Levels for PSB202

Level	Dose	Frequency
1 (starting dose)	12 mg	D1, D8, and D15 of Cycle 1 (loading doses), then D1 of each subsequent cycle (21-day cycles)
2	36 mg	
3	100 mg	
4	300 mg	
5	600 mg	
6	1000 mg	
7	1500 mg	
8 and higher	~ 33% increase	

Escalation to dose levels higher than 2500 mg is not planned under this protocol.

A steroid is recommended to be added to the pre-medication regimen as per institutional pre-medication standard of care. Standard pre-infusion medications (650-1000 mg acetaminophen and anti-histamine) will be provided 30-60 minutes prior to study drug infusion. For clinics preferring IV pre-medication, a glucocorticoid (10-20 mg dexamethasone or 40-80 mg methylprednisolone or equivalent other steroid), along with an anti-histamine, may be provided prior to PSB202 infusions. Patients deemed at increased risk for tumor lysis syndrome (high tumor burden, absolute lymphocyte count $\geq 25 \times 10^9$ /L

will be provided with anti-hyperuricemics (e.g. allopurinol or rasburicase) pre-infusion. PEPCID and supplementary hydration may be added per investigator discretion.

A meeting of the SRC will be convened for each phase 1a dose escalation decision (excepted accelerated titration dose level). Other than when a DLT occurs and stops further dosing, each patient in a cohort must have completed safety assessments through the first 28 days of study drug and must have received at least 3 of 4 planned doses (D1, D8 and D15 of Cycle 1 and/or D1 of Cycle 2) to be deemed evaluable for DLT. Patients who receive LESS than 3 of the planned 4 doses due to reasons other than a DLT will be replaced for the determination of the MTD but will remain part of the safety population if they received at least 1 dose of study drug. Any toxicity in the first 28 days causing a missed dose or dose-delay to result in receipt of less than 75% of the planned 4 doses (i.e. receipt of less than 3 of 4 study drug administrations -planned during the DLT-period) will be reviewed by the SRC and will be considered a DLT if the SRC determines the toxicity cannot be attributed to the patient's underlying disease, other medical condition or concomitant medications. In other words, absent toxicity, a single missed or delayed dose (i.e. 1 of 4 planned doses is missed or delayed) will not render a patient non-evaluable for DLT. Notwithstanding aforementioned, in Phase 1a, dose reduction is not allowed during the DLT period.

One to 6 patients in each cohort must have completed 28 days of safety assessment in Cycle 1 without a DLT, and the DLT rate must be <33% (i.e., 0 of 1, 0 of 3, or 1 of 6 patients), before the next cohort initiates accrual. In addition, guided by review of all safety data including any safety signals emerging during treatment beyond the period, SRC may determine that additional patients should be evaluated at an intermediate dose level lower than the highest dose reached during escalation. Alternative dosing schedules such as step-up dosing or priming dose may also be recommended for evaluation within the 3+3 framework. Escalation will proceed through all dose levels or until the Sponsor and SRC determine that a suitable dose has been achieved based on available data (PK, safety, pharmacodynamic and clinical activity)

After completion of the DLT period, intra-patient dose escalation may be approved by the Sponsor Medical Monitor, provided that the patient is tolerating his/her current dose, and the dose level to which the patient will be escalated has a DLT rate <33% and has been cleared as safe by the SRC. Patients who are dose-escalated in this way will not be counted as "backfill patients" as described in the subsequent paragraph, but are evaluated for safety at the higher dose level. Patients in the lowest (single-patient) cohorts may be dose-escalated to the last 3-patient cohort deemed safe by the SRC. Other patients may be dose escalated in single dose-level increments to the next higher dose level cleared as safe by the SRC.

During phase 1a, cohorts at dose levels previously declared safe by the SRC may be expanded with up to 5 "backfill" patients to further investigate the tolerability, PK, and

biological activity of PSB202. During Phase 1a, enrollment of patients to the open dose escalation cohort will take precedent. The SRC will continue to monitor the cumulative safety data from cohorts previously declared safe and the current dose cohort under evaluation.

Escalation will proceed through ascending dose levels or until the SRC and the Sponsor determine that a suitable dose has been achieved based on available data (safety, PK exposure, clinical activity).

Dose-limiting Toxicity (DLT) Definition:

A DLT is defined as any of the treatment-emergent adverse events (TEAEs; a TEAE is defined as an adverse event [AE] that start on or after the first dose of study drug) listed below, as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5 (NCI CTCAE v5), and for hematologic adverse events in CLL patients, IWCLL criteria for hematologic toxicity (Hallek, Cheson et al. 2018), occurring during the first 28 days of study drug, and the AE is not reasonably attributed to the patient's underlying disease, other medical condition or concomitant medications. The DLT definitions are:

1) Any ≥ Grade 3 non-hematologic toxicity **except for**:
   - Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and/or total bilirubin elevation for ≤8 days. However, any combination of laboratory abnormalities meeting Hy's Law criteria for drug-induced liver toxicity will be considered a DLT.
   - First occurrence of Grade 3 electrolyte abnormalities and/or creatinine clearance decrease resolving to Grade 2 (or baseline if baseline is ≥Grade 2) within 48 hours with supportive treatment
   - Grade 3 fatigue, nausea, vomiting, diarrhea as long as it does not necessitate hospitalization, TPN, or tube feeding.
   - Grade 3 infusion reaction (rigors, chills, muscle spasms etc.), unless unresolved after 24 hours
   - Grade 3 infection responding to appropriate antibiotic/anti-viral therapy.
   - Any Grade 3-4 asymptomatic laboratory abnormality that is not clinically significant and does not require therapeutic intervention
2) Any ≥ Grade 3 hematologic toxicity will be considered a DLT **except for**:
   - Grade 3 neutropenia without fever
   - Neutropenic fever resolved within 48 hours with appropriate antibiotic- and medical management

- Grade 4 neutropenia without fever lasting 10 days or less
- Grade 3/4 thrombocytopenia that does not result in bleeding. Grade 4 thrombocytopenia lasting ≥7 days is a DLT.
- Grade 3/4 lymphopenia/lymphocytosis
- Grade 3/4 white blood cell (WBC) decreased

3) Grade 5 (fatal) toxicity

4) Grade 3 or 4 cytokine release syndrome

5) Any toxicity, regardless of the NCI CTCAE v5.0 grade, resulting in discontinuation, dose delay or treatment with less than 75% of planned doses (i.e. receipt of less than 3 of 4 doses planned during the DLT-period), will be reviewed by the SRC, and will be considered a DLT if occurring during the DLT-observation period (Day 1-28) provided the SRC determines the toxicity cannot be attributed to the patient's underlying disease, other medical condition or concomitant medications.

Phase 1b Design:

Once the MTD or RP1b-Dose is identified, ~20 patients with various indolent NHL histologies and WM will be enrolled to one of the following cohorts. Patients who discontinue early may be replaced with the aim to enroll and retain ~ 20 patients evaluable for response (W16 response evaluation) in each cohort. In the opinion of the investigator, patients must have exhausted available standard-of-care options and require systemic therapy based on disease-specific criteria (see Appendices C, D, E).

- Cohort 1: FL, progressed within 6 months after at least two regimens, at least one of which contained anti-CD20 antibody (i.e. single-agent R or R-chemo)
- Cohort 2: CLL/SLL failed two or more prior lines of therapy
- Cohort 3: WM, MZL, MCL failed at least 2 prior regimens; MCL must have received previously received an alkylating agent.

Successfully accruing cohorts may be expanded with up to 20 additional patients. Cohort expansion is conditioned on patients initially enrolled in the cohort to have shown a response rate higher than the futility proportion (See Section 8.3). Details will be provided in a separate Statistical Analysis Plan prior to commencement of Phase 1b.

In Phase 1a and 1b, all patients should have documented CD20+ expression based on previous pathological reports prior to dosing. In Phase 1a, CD37+ expression will be recorded in the CRF if available from the patient chart, but will not be required if not available. For Phase 1b, CD37 status must be known to allow exploratory analyses, but both CD37+ and CD37- patients may be enrolled. Archival reports and/or material may be

used for documentation of CD37+ status, but in case no archival CD37+ result or library specimen is available, new sampling will be performed pre-dosing, and should be evaluated for CD20 and CD37 by a laboratory with certification by Clinical Laboratory Improvement Association (CLIA), International Organization for Standardization/Independent Ethics Committee (ISO/IEC), College of American Pathologists (CAP), or equivalent. Dosing need not await reporting of the result of confirmatory CD37+ testing. Hence, confirmation of CD37+ status is optional, but CD20+ positivity is always required.

Patients treated during dose escalation (Phase 1a) at the MTD/RP1b Dose who also meet the criteria for one of the Phase 1b cohorts may be considered as part of the evaluable patients for that cohort.

ELIGIBILITY CRITERIA:

Inclusion Criteria:

Phase 1a (dose escalation):

1. Histologically confirmed CD20+ expressing indolent NHL (defined below), CLL or WM, failed or intolerant to standard of care therapies;
2. Relapsed/refractory following at least 2 prior lines of standard of care treatment. Prior treatments received must be documented on the enrollment request form. For FL, prior treatment must have included at least 1 rituximab containing regimen.
3. First three dose levels: in the opinion of the investigator, able to tolerate potentially subtherapeutic doses of PSB202 for the duration of the DLT observation window.

Phase 1b – Dose Expansion:

4. Histologically confirmed CD20+ expression. For CD37+, if unavailable from the chart at screening, CD37+ expression may be documented from a new or archived blood specimen after enrollment.
5. Relapsed indolent NHL: histologies that may be included are CLL/SLL, MZL/ MALT, FL1-3a, MCL (indolent subtype) or WM failed, relapsed/refractory or intolerant to at least 2 standard of care therapies. (APPENDIX B). For FL, prior treatment must have included anti-CD20 antibody. MCL must have received a prior alkylating agent.
6. Patients must have documented disease progression after at least

two prior standard-of-care regimens.

All Patients:

7. Signed Informed Consent;
8. Eastern Cooperative Oncology Group (ECOG) 0-2
9. Last dose of any anti-CD20 antibody therapy must have been >4 weeks before the first dose of PSB202
10. Patients with a medical history of Covid-19 positivity at any time prior to enrollment, must be retested within 7 days of enrollment and confirm Covid-19 negativity by a PCR-test.
11. At least 18 years of age. There is no upper age restriction.
12. Patients in Phase 1b must have measurable disease (excepted CLL and WM).
13. Four weeks wash-out from any other prior cancer therapy, including rituximab or BTK-inhibitors. However, some heavily pretreated patients are at risk for significant morbidity from accelerated disease progression or "flare" when treatment is discontinued prior to the initiation of subsequent effective therapy. Absent residual toxicity and with documented Medical Monitor approval, such patients may receive study drug after five drug half-lives have passed following discontinuation of the immediate pre-study therapy.
14. Adequate hematologic and coagulation status, defined as the following (See Table 6):
    - Absolute neutrophil count (ANC) $\geq 0.75 \times 10^9$/L and not requiring growth factors.
    - Platelet count $\geq 75 \times 10^9$/L not requiring transfusion support; if there is documented bone marrow involvement, platelet transfusions may be used up to 7 days prior to C1D1 to achieve this threshold.
    - Hemoglobin (Hb) $\geq$ 9 g/dLnot requiring transfusion support or growth factors.
    - Adequate coagulation, defined as aPTT and PT (or INR if PT is not done) not greater than 1.5 $\times$ upper limit of normal (ULN) (patients appropriately anticoagulated for a

preexisting medical condition [e.g., atrial fibrillation] may be eligible with documented Sponsor approval).

15. Adequate hepatic and renal function, defined as:
    - ALT or AST ≤2.5 × the ULN or ≤5 × ULN with documented liver involvement.
    - Total bilirubin ≤1.5 × ULN or ≤3 × ULN with documented liver involvement and/or Gilbert's Disease
    - with expected creatinine clearance (Ccr, equation as below) or estimated glomerular filtration rate (eGRR)via Cockcroft-Gault equation ≥50 mL/minute.

$$\text{Ccr} = \frac{(140-\text{Age}) \times (\text{Weight/kg}) \times 0.85(\text{if female})}{72 \times \text{serum creatinine (mg/dl)}}$$

Or

$$\text{Ccr} = \frac{(140-\text{Age}) \times (\text{Weight/kg}) \times 0.85(\text{if female})}{0.818 \times \text{serum creatinine } (\mu\text{mol/L})}$$

16. Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
17. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following the last dose of study treatment; this may include barrier methods such as condom or diaphragm with spermicidal gel.

Exclusion Criteria

Phase 1a (dose escalation) only:

1. NHL with bulky disease defined as a mass ≥10 cm in longest diameter
2. Transformation (e.g., Richter's transformation, prolymphocytic leukemia, transformed NHL, blastoid lymphoma) prior to planned start of PSB202. In addition, no concurrent investigational therapy is permitted.

All patients: 1a (dose escalation) and Phase 1b (expansion):

3. Major surgery within 4 weeks prior to planned start of PSB202
4. Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for 13patients receiving radiation to more

than 30% of the bone marrow or receiving whole brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment

5. Continuation of certain standard of care anticancer therapies, including hormonal therapy for breast and prostate cancer, and growth factor support after completion of the DLT-period, is allowed.
6. Any unresolved toxicities from prior therapy greater than CTCAE (version 5.0) Grade 2 or greater at the time of starting study treatment except for alopecia.
7. History of autologous stem cell transplant (auto-SCT) or autologous chimeric antigen receptor-modified T-cell (CAR-T) therapy within the past 180 days with any of the following: cytopenias from incomplete blood cell count recovery post-transplant, need for anti-cytokine therapy, residual symptoms of neurotoxicity > Grade 1, or ongoing immunosuppressive therapy.
8. Active graft versus host disease (GVHD, including rejection resultant from any prior solid organ transplants, if received), or ongoing immunosuppressive therapy.
9. History of allogeneic stem cell transplant (allo-SCT) or allogeneic CAR-T at any time in the patient's medical history
10. Known central nervous system (CNS) involvement by lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable and without evidence of active CNS-disease may be eligible if a clinical rationale is provided by the Investigator and with documented Sponsor approval
11. Active auto-immune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP])
12. Cerebrovascular accident (CVA), Transient ischemic attack (TIA), myocardial infarction, unstable angina, or New York Heart Association (NYHA) class III or IV heart failure < 6 months of study screening; mean ECG QT-interval corrected according to Fridericia's formula (QTcF) > 450 milliseconds (ms) (males) or > 470 ms (females) obtained from three ECGs; uncontrolled arrhythmia < 3 months of study screening. Patients with rate-controlled arrhythmias may be eligible for study entry at discretion of the Investigator.
13. Active uncontrolled systemic bacterial, viral, fungal or parasitic infection (except for fungal nail infection), or other clinically significant active disease process which in the opinion of the Investigator and the Sponsor makes it undesirable for the patient to participate in the trial. Screening for chronic conditions is not required.
14. Tested positive for Human Immunodeficiency Virus (HIV) is excluded (due to

potential drug-drug interactions between anti-retroviral medications and PSB202 and risk of opportunistic infections). For patients with unknown HIV status, HIV testing will be performed at Screening

15. Active viral hepatitis (B or C, HBsAg, anti-HBs/HBcAb and anti-HCV Ab tests) as demonstrated by positive serology or requiring treatment. Subjects who are anti-HBs/HBcAb (+) without detectable HBV-DNA are eligible. Subjects with a history of Hepatitis C and have received successful curative treatment are eligible.
16. Pregnancy or lactation.
17. Active autoimmune disease or history of autoimmune disease requiring systemic therapy < 2 years prior to screening except hypothyroidism, vitiligo, Grave's disease, Hashimoto's disease, or Type I diabetes. Patients with childhood asthma or atopy that has not been active in the 2 years prior to study screening are eligible.
18. History of drug-induced liver injury or cirrhosis
19. History of drug-related pneumonitis or interstitial lung disease
20. Patients with significant medical diseases or conditions, as assessed by the Investigator and Sponsor, that would substantially increase the risk-benefit ratio of participating in the study. Active second malignancy unless in remission and with life expectancy >2 years.

PLANNED SAMPLE SIZE:

Phase 1a – Dose Escalation: Including backfill patients, approximately 32-40 patients in Phase 1a of the study. This includes ~12 patients to complete 6 each for CLL and non-CLL histologies, to define the MTD/recommended Phase 1b dose and further study of PSB202, and ~ 20-28 patients to lower dose levels, including backfill to dose levels determined safe by the SRC. This assumes no more than 8 dose levels will be evaluated. The actual number of doses levels can be lower if MTD is reached at a lower dose.

Phase 1b – Dose Expansion: Up to 20 patients for each cohort for up to 60 patients across 3 cohorts. Expansion beyond 20 patients in any cohort is conditioned on achieving a response rate above the futility threshold in the initial patients enrolled in the cohort, as shall be detailed in a separate Statistical Analysis Plan prior to commencement of Phase 1b. **Total:** ~92-100 patients may be enrolled in the study: approximately 32-40 in Phase 1a and up to 60 in Phase 1b.

INVESTIGATIONAL PRODUCT:

PSB202 will be provided as a sterile solution in 15 mL vials with 8 mL fill. The vials will be provided to the sites for outpatient clinic administration at the assigned dose level. Dosing is intended to be fixed (i.e., not weight-based or body surface area-based).

TREATMENT PROCEDURES:

Patients will begin dosing on Cycle 1 Day 1 (C1D1) according to the assigned cohort. In Phase 1a and Phase 1b, cycle length will be 21 days, with two extra loading doses (D8 and D15) in Cycle 1 only. PSB202 will be administered only on Day 1 of subsequent cycles. Individual patients will continue PSB202 dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation.

STUDY ASSESSMENTS:

The Schedule of assessments and procedures for the study is provided in Table **6**.

Safety observations include physical and neurological examination, body weight, ECOG score, clinical AEs, laboratory variables (hematology, serum chemistries, and urinalysis), ECGs and vital signs. In Phase 1a, during the DLT period (D1-28), clinic visits are scheduled weekly. Subsequent cycle visits coincide with the study drug infusion day, with an additional clinic visit prior to the end of each cycle when tumor response assessment is due, as it may not be feasible to schedule all response evaluation procedures on the same day as study drug infusion.

Tumor evaluations are conducted at every 3 cycles (±7 days) since first dose, such as C3D1 ±7 days (week 7 ±7 days), C6D1 ±7 days (week 16 ±7 days), C9D1 ±7 days (week 25 ±7 days). After completing 9 cycles of treatment, tumor evaluation should be conducted every 12 weeks (±14 days) up to 2 years or the end of the study. All the measurable and evaluable lesions should be assessed and documented at screening, and re-assessed at each subsequent tumor evaluation, using hematological test, physical examination and CT scan (neck, thorax, abdomen and pelvis) for contrast-enhanced CT scan. Magnetic resonance imaging (MRI) or a PET-CT scan (only FDG-avid subtypes such as FL and MCL) may be used instead of CT scan for the patients with contraindications to CT scan. A confirmatory tumor evaluation after the first tumor evaluation that shows a CR o by disease-specific criteria, if consistent with local regulatory authority requirements, combine bone marrow aspirate and/or biopsy with PET-CT scan should be used together with a contrast-enhanced CT scan, instead of CT scanning based on clinical practice.

In Phase 1b, information related to response assessments (e.g., scans, bone marrow and peripheral blood samples where applicable) will be collected and stored at a central facility to permit for later independent review. Patients with a clinical CR will be evaluated for MRD.

An End of Treatment (EOT) visit is required within 7 days after the last dose of PSB202 or

the decision to terminate PSB202 treatment. The safety follow-up (SFU) assessments will be conducted within 3 weeks (+14 days) of last dose of study drug. If feasible, this visit may coincide with EOT tumor response evaluation. Unless consent for any further follow-up is withdrawn, all patients, including those no longer on study drug, will enter Long-term Follow-up (LTFU) with visits ~ every 3 months (± 14 days) until 2 years or study closure, whichever comes first, to confirm the resolution of any SAEs, PD if not occurring on while on study-drug, documentation of any subsequent anticancer therapy, and survival. LTFU may be conducted by phone if unable to travel to clinic.

Patients who discontinue study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy, will continue undergoing disease assessment as appropriate to histology (as specified above) until PD, withdrawal of consent, or initiation of a new anticancer therapy until 2 years or end of study, whichever occurs first.

During Phase 1a only, blood for PK assessment will be collected on different time points as detailed in the Study Schedule (Table 6). Patients who undergo intra-patient dose escalation should undergo PK-assessment on Day 1 (3 time points) of the new dose. For patients with multiple dose escalations, PK is required following the first dose escalation only.

At Phase 1b study entry, tumor samples (i.e., bone marrow, peripheral blood leukemia/lymphoma cells, and/or lymph node/tumor biopsy depending on diagnosis) may be obtained for patients and banked by the Sponsor. Samples for sparse PK will be obtained as outlined in the Schedule of Assessments table. Guidance is provided in the Laboratory Manual.

STUDY ENDPOINTS:

Primary Endpoint (Phase 1a):

- The Dose Limiting Toxicities DLT, guiding establishment of a MTD/RP1b Dose/recommended dose for further study.

Secondary Endpoints (Phase 1a):

- Adverse events and serious adverse events, changes in hematology and blood chemistry values, ADA, vital signs, and ECGs.
- Plasma concentration of PSB202 and PK parameters including, but not limited to area under the concentration versus time curve (AUC), maximum drug concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life ($T_{1/2}$), and degree of accumulation.
- ORR by Investigator: Best ORR at any given time during treatment

Primary Endpoint (Phase 1b; for each cohort):

- ORR by Investigator

Secondary Endpoints (Phase 1b; for each cohort):

ORR (by IRC), BOR, DOR, PFS (by Investigator and IRC)

Adverse events and serious adverse events, changes in hematology and blood chemistry values, ADA, assessments of physical examinations, vital signs, and ECGs.

Plasma concentration of PSB202 and PK parameters including, but not limited to AUC, C_{max}, T_{max} (time to maximum plasma concentration), $T_{1/2}$, and degree of accumulation.

Exploratory Endpoints (Phase 1a and Phase 1b for each cohort):

Differences in efficacy and safety based on PSB202 PK parameters.

MRD for those CLL/SLL patients with a clinical CR

In FL patients only: peripheral blood *bcl-2* re-arrangement (reversion to negative).

STATISTICAL METHODS:

Safety Analyses:

The safety population will consist of all enrolled patients who receive at least 1 dose of PSB202. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after the start of study drug may be required for inclusion in the analysis of a specific safety parameter.

An SRC, comprised of the enrolling PIs and the Sponsor MM, will be established to oversee the safety aspects of the phase 1a portion of the study. The SRC will perform ongoing review of SAEs and other safety-related data throughout the conduct of the study. For phase 1a, the SRC will be convened for each dose escalation decision or as needed. For phase 1b, the SRC will convene at a minimum of once every 6 months.

Effectiveness (Response) Analyses:

The primary analysis of efficacy will be based on the Full Analysis Set (FAS) which will include all patients who receive at least 1 dose of study drug and have measurable disease at baseline by disease-defined criteria. These analyses will be summarized by the specific B-cell malignancy (e.g., CLL/SLL, FL, WM, MCL, MZL and the status of specific tumor gene mutations (e.g., peripheral *bcl-2* status in FL-patients). Patients who meet phase 1b eligibility, but who were enrolled in the phase 1a portion at the dose level later chosen as the Phase 1b dose, may be included in the phase 1b efficacy analyses.

ORR will be assessed using IWWM (Appendix D) or Lugano criteria (Appendix E), as appropriate to tumor type. The estimate of the ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with BOR of PR or better,

based on IWWM or Lugano criteria as determined by IRC and by the treating Investigator. The estimates of the ORR will be accompanied by a 2-sided 95% confidence interval (CI). Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of product diameters (SPD) of target lesions. The duration of overall response, ETR and PFS will be summarized descriptively for each cohort using the Kaplan-Meier method.

Pharmacokinetic Analyses:

During Phase 1a, plasma concentrations of PSB202 will be determined with a validated bioanalytical assay. The following PK parameters will be calculated from plasma concentrations determined on C1D, C1D8 and C1D15 on 3 time points (pre-dose; 15 minutes after end-of-dosing; 2 hrs after end-of-dosing), and C3D1 and C6D1 (pre-dose only), if appropriate: C_{max}, T_{max}, AUC_{0-t} (area under the concentration vs time curve from time 0 to t), $AUC_{0-\infty}$, apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), and $T_{1/2}$.

Summary statistics will be generated by dose cohort and across cohorts as appropriate.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition
AE	adverse event
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration vs time curve
$AUC_{0-\infty}$	area under the concentration versus time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration versus time curve from time 0 to t
AUC_{0-24}	area under the concentration versus time curve from time 0 to 24 hours
AUC_{tau}	area under the concentration versus time curve calculated during the dosing interval at steady state
BCR	B cell receptor
BOR	best overall response
BUN	blood urea nitrogen
BSA	body surface area
BTK	Bruton's tyrosine kinase
C1D1	Cycle 1 Day 1
CAP	College of American Pathologists
CAR-T	chimeric antigen receptor-modified T cells
CDMS	Clinical Data Management System
cfDNA	circulating free tumor deoxyribonucleic acid
CI	confidence interval
CL/F	apparent oral clearance of drug
CLIA	Clinical Laboratory Improvement Amendments
CLL	chronic lymphocytic leukemia
C_{max}	maximum drug concentration
C_{min}	minimum drug concentration
CNS	central nervous system
CR	complete response
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450
D	Day
DLBCL	diffuse large b cell lymphoma
DLT	dose-limiting toxicity

Abbreviation or Term	Definition
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone
GVHD	graft versus host disease
H2	histamine type-2
Hb	Hemoglobin
HED	human equivalent dose
hERG	human ether- à-go-go related gene
HIV	Human Immunodeficiency Virus
HR	heart rate
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICH GCP	International Conference on Harmonisation-Good Clinical Practices
IEC	Independent Ethics Committee
IP3	inositol 3-phosphate
IRB	Institutional Review Board
IRC	Independent Review Committee
ISO/IEC	International Organization for Standardization/ Independent Ethics Committee
ITP	idiopathic thrombocytopenic purpura
IV	Intravenous
LDH	lactate dehydrogenase
LDi	longest diameter

Abbreviation or Term	Definition
LHRH	luteinizing hormone-releasing hormone
LTFU	Long-term Follow-up
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MR	minor response
MRD	minimal residual disease
MRI	magnetic resonance imaging
MRSD	maximum recommended starting dose
MTD	maximum tolerated dose
mRNA	messenger ribonucleic acid
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NHL	non-Hodgkin's lymphoma
NOAEL	no-observable-adverse-effect-level
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PEPCID	Famotidine
PFS	progression-free survival
P-gp	p-glycoprotein
PI3K	PI3-kinase
PIP3	phosphatidylinositol 3-phosphate
PK	pharmacokinetic
PLCg2	phospholipase C gamma 2
PO	per os (oral)
PP	Per-protocol Analysis Set
PPI	proton pump inhibitors
PR	partial response
PSB202	investigational product
PT	prothrombin time
QD	once daily
QTcF	QT interval corrected for heart rate (Fridericia's formula)
RBC	red blood cell

Abbreviation or Term	Definition
REB	Research Ethics Board
R/R	relapsed/refractory
RP1bD	recommended Phase 1b dose
RT	Richter's Transformation
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCT	stem cell transplant
SD	stable disease
SERDs	selective estrogen receptor degraders
SERMs	selective estrogen receptor modulators
SFU	Safety Follow-up
SLL	Small Lymphocytic Lymphoma
SOC	system organ class
SPD	sum of product diameters
SRC	Safety Review Committee
STD 10	severely toxic dose in 10% of the animals
SUSARs	suspected unexpected serious adverse reactions
$T_{1/2}$	terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
TBD	to be determined
TEAE	treatment-emergent adverse event
TEC	Tec kinase
TKIs	tyrosine kinase inhibitors
T_{max}	time to maximum plasma concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VGPR	very good partial response
V_z/F	apparent volume of distribution
WBC	white blood cell
WBRT	whole brain radiation therapy
WM	Waldenström macroglobulinemia
Y551	tyrosine residue 551

1 INTRODUCTION

1.1 CD20+ and CD37+ expressing Malignancies

CD20 and CD37 are co-expressed on most B cell non-Hodgkin's lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL) tumors (Deckert et al., 2013). CD20 is a lineage-specific target, while very low levels of CD37 have been reported in other hematopoietic cell types. Systemic depletion of normal and malignant B-cells by anti-CD20 antibodies (e.g. rituximab and obinutuzumab) and anti-CD37 antibodies (e.g. otlertuzumab and BI 836826) has been tolerated in clinical studies. B-cell depletion is reversible, with the ability to repopulate B-cells from hematopoietic stem cells.

PSB202 is a novel biological entity consisting of two engineered monoclonal antibodies, an Fc-enhanced humanized type II anti-CD20 IgG1 (PSB102) and a humanized anti-CD37 IgG1 (PSB107), that target B-cells. PSB202 is manufactured to work as a single product with the two components of PSB202 enabling a distinct dual target-specific antibody directed cell killing of B-cells.

PSB202 has been developed to mediate B cell killing and depletion through multiple mechanisms. PSB102 can kill B cells directly, by homotypic adhesion formation and activation of signaling, similar to other type II mAbs, including obinutuzumab (Gazyva). PSB107 also exhibits potent direct B cell killing which is not dependent on CD37 cross-linking. PSB102 and PSB107 have been developed to kill B cells through additional Fc-mediated effector mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). These activities should be combinatorial and are improved further through modification of mAb glycosylation, including reduced fucosylation. PSB102 is engineered, through single point mutations within the Fc region, to have enhanced ADCC activity compared to wildtype IgG1. However, PSB107 lacks the same engineering. PSB202 is produced in the presence of an L-fucose analog, 2-fluoro-L-fucose (2FF), which inhibits fucosylation, producing antibodies with reduced fucose levels. Reducing antibody fucose levels selectively improves IgG1 binding to FcγRIIIa and leads to greater ADCC, especially for PSB107.

Unlike approved antibodies, such as obinutuzumab and rituximab, that target only a single cell surface protein, PSB202 can have killing activity against cells that express CD20 and/or CD37. For tumorigenic B cells that potentially express both CD20 and CD37, the B cell depleting activity exhibited by PSB202 has the potential to be combinatorial, resulting in efficacy that is similar, or superior, to antibodies that target only CD20 or CD37. This is supported by early phase clinical studies demonstrating the safety and efficacy of anti-CD37 mAbs otlertuzumab and BI 836826 in treating CLL, NHL, and Waldenström macroglobulinemia (WM), both alone and in combination with bendamustine (Byrd et al., 2014; Stilgenbauer et al., 2019; Robak et al., 2016). Further, B-cell malignancies that are refractive or have relapsed to single agent targeting antibodies that target CD20 or CD37

have the potential to still be targeted by the activity of PSB202 which targets both CD20 and CD37.

1.2 PSB202

A summary of the properties and nonclinical findings of PSB202 is provided in 1.2.1 and 1.2.2. Additional information on the nonclinical pharmacology, pharmacokinetics (PKs) and toxicity of PSB202 are provided in the PSB202 IB.

1.2.1 Chemistry and Description

PSB202 is an antibody combination product comprised of a 1:1 blend of two full-length monoclonal antibodies, PSB102 and PSB 107 respectively targeting CD20 and CD37.

1.2.2 Nonclinical

The pharmacology, PK, and toxicology programs were designed to characterize the nonclinical efficacy, disposition, and safety of PSB202 and to enable selection of an appropriate starting dose for this Phase 1 clinical study. These are described in detail in the PSB202 IB.

1.2.2.1 Primary Pharmacodynamics

In vitro studies: Binding activity studies demonstrated the ability of PSB202 to bind human CD20 and CD37 antigens in both recombinant CHO cells and in various types of malignant B-cells. The PSB102 antibody exhibited comparable binding activity to CD20 antigens in both human and cynomolgus monkey CD19+ B-cells (EC50 2.878 nM and 1.689 nM, respectively), while PSB107 was strictly specific to human CD37 antigen (EC50=1.327 nM). No binding to rat, rabbit or beagle dog antigens was observed. The specificity of the Fc fragment for FcγRIIIa was demonstrated to have a higher binding affinity for human FcγRIIIa (CD16a) (K_D ~0.82 nM) compared to lower binding affinities for other Fcγ receptors. In addition, significant binding was observed for the human FcγRI receptor (CD64) (K_D=0.074 nM). These findings demonstrate that in addition to FcγRIIIa-mediated NK cell activation, a strong binding affinity for FcγRI may suggest a potential involvement of monocytes in the mechanism of PSB202 effector-mediated cytotoxicity. PSB202 and its components, PSB102 and PSB107, demonstrated a potential to stimulate NK-mediated cytotoxicity followed by depletion of human and monkey CD20/CHO and CD37/CHO cells and malignant human B-cells, through the involvement of ADCC (EC50=0.0087 nM) and to a much lesser potency, of CDC mechanisms (EC50=3.08 nM). PSB202 also demonstrated the ability to induce cytotoxicity via CD20 and CD37 receptor cross-linking in various human lymphoma cell lines; however, to a lesser extent compared to ADCC mediated cytotoxicity (IC50= 0.56-5.05 nM). PSB202 and its component, PSB107, demonstrated a robustly enhanced CD19+ B-cells depleting activity (52.00% and 39.30%, respectively) in the blood sample of relapsing follicular lymphoma (FL) patient, compared to obinutuzumab (22.06%) and rituximab (15.61%). PSB202 also demonstrated

comparable potency to obinutuzumab with marginal zone lymphoma (MZL) cells (39.94% vs. 23.70%, respectively). Importantly, PSB202 demonstrated a much higher level of maximum B cell depletion (44.92%) than other CD20 antibodies such as obinutuzumab (26.71%) or rituximab (13.94%) in CLL patient with relapsing disease that were treated previously with rituximab.

In vivo experiments demonstrated that PSB202 administered twice a week (BIW) for up to four weeks was able to reduce Daudi tumor growth by up to ~97.9% at a dose level of 20 mg/kg via the i.p. route, Ramos tumor growth by up to ~86% at dose level of 2 mg/kg via the i.p. route, and Raji tumor up to ~52% at a dose of 10 mg/kg via the *i.v.* route, and in a dose-dependent manner. Combinational treatment of Raji tumor with *i.v.* administration at 10 mg/kg PSB202 (BIWx4) and daily oral (p.o.) administration of 50 mg/kg lenalidomide (QDx28) demonstrated a synergistic effect of tumor growth inhibition (~80%) compared to PSB202 (52%) or lenalidomide alone (4%). Lenalidomide is a small molecule that modulates of the substrate specificity of an E3 ubiquitin ligase with downstream killing of multiple myeloma cells.

1.2.2.2 Secondary Pharmacodynamics

No secondary pharmacology studies were conducted.

1.2.2.3 Pharmacokinetics

Following a single *i.v.* administration of at 3, 10, or 30 mg/kg of PSB202 via *i.v.* infusion in male monkeys (3/group), systemic exposure (Cmax and AUC) of PSB102 was positively correlated with dose levels across groups with non-linear kinetics. The calculated AUC per dose was 1070, 5870 and 32300 μg•h/mL at 3, 10 and 30 mg/kg, respectively. The average T1/2 across the dose range of 3-30 mg/kg of PSB102 varied from 37.6 to 61.6 h with a tendency to increase in a dose dependent manner for the first two dose levels. CL was 0.933-2.73 mL/h/kg. The apparent volume of distribution (Vz) was 82.5-145 mL/kg.

For PSB107, the systemic exposure increased dose-dependently, with a tendency for non-linear kinetics. The calculated AUC per dose was 1640, 6810 and 22000 μg•h/mL at 3, 10 and 30 mg/kg, respectively. The average T1/2 across the range of 3-30 mg/kg of PSB107 varied from 40.0 to 72.8 h with tendency to increase in dose dependent manner. CL was 0.27-1.65 mL/h/kg. The apparent volume of distribution (Vz) was 118-139 mL/kg.

Following once weekly *i.v.* infusions of PSB202 in cynomolgus monkeys at a dose of 0, 10, 50, and 200 mg/kg for 4 weeks for a total of 5 doses, the serum concentrations of animals in the 10 mg/kg, 50 mg/kg, and 200 mg/kg groups were positively correlated with dosage for both components of PSB202, in the 1st and 4th dosing period and without obvious gender differences. On Day 29, anti-PSB202 antibodies (ADA) formed in 29% of the all PSB202-treated animals, mainly in the 10 mg/kg group (8/10, 86% of all ADA positive cases), on Day 29. Two animals in this group were ADA positive in the first week

of treatment (pre-dose). One ADA positive male was detected in 50 mg/kg dose group. No ADA positive animals were detected in the 200 mg/kg group.

After the 4th dosing (Day 22), the systemic exposure for PSB102 in the 10 mg/kg group dropped to ~20% of its value after the 1st dosing in males and to 14% in females, possibly due to ADA formation. The AF (accumulation factor: AUC_{last}，D22/AUC_{last}，D1) of 0.97, and 1.42, in males and 0.99, and 1.72 in females was determined for 50 and 200 mg/kg dosing groups, respectively. The systemic exposure for PSB107 in the 10mg/kg group has dropped to ~12% of its value after the 1st dosing in males and to 1.2% in females, which could be attributed to the ADA formation in this group. The AF of 1.07 and 1.02 in males, and 0.59, and 1.37 in females was determined for 50 and 200 mg/kg dosing groups, respectively. No apparent drug accumulation was noted at any of the dosing groups.

1.2.2.4 Drug Interactions

No pharmacokinetic drug interaction studies were conducted. The expected in vivo degradation of antibodies is via biochemical pathways that are independent of CYP enzymes. Consequently, typical antibodies, such as PSB202, are not expected to interact with molecules that are metabolized by these enzymes.

1.2.2.5 Safety Pharmacology

Based on the PSB202, CD20 and CD37 binding activity profile and monkey B-cell depletion results, cynomolgus monkey has been determined to be the only pharmacologically relevant species. Safety pharmacology was evaluated as part of a GLP-compliant, repeat-dose toxicology study wherein animals received *i.v.* administrations of PSB202 each of 0, 10, 50, or 200 mg/kg, once a week (QW) for 4 weeks. No abnormalities in electrocardiogram, including rhythm, waveform morphology, or apparent functional changes were observed in the animals.

1.2.2.6 Toxicology

In single-dose toxicology study, no test article-related changes in clinical observations, body weight, food consumption, coagulation, clinical chemistry, and urinalysis were observed at male cynomolgus monkeys that were administered PSB202 at 3, 10, or 30 mg/kg via *i.v.* bolus and observed for 28 days post dosing. PSB202-related changes in hematology parameters were noted on Day 2 at ≥ 3 mg/kg resulting in decreases in the WBC count and large unstained cells (LUCs), that tended to return to baseline on Day 7. PSB202 administration at ≥ 3 mg/kg resulted in dose-independent, nearly complete depletion in B-lymphocytes, and natural killer cells on Day 2 through Day 15. Additionally, total T-, T-helper (Th-), and T-cytotoxic (Tc-) lymphocytes were also decreased in a dose-independent manner at all dose levels on Day 2 through Day 15. The

changes in the cell populations generally trended towards or returned to the pre-study baseline on Day 29.

In the pivotal 28-day repeat-dose toxicology study in cynomolgus monkeys administered 0 (vehicle), 10, 50, or 200 mg/kg of PSB202, QW×5 via *i.v.* infusion, two female animals at 10 mg/kg dosing group and one male at 200 mg/kg dosing group were prematurely euthanized due to declining clinical condition that was attributed to immune-mediated infusion reactions, likely associated with ADA formation.

In the surviving animals, PSB202-related clinical pathology changes at ≥ 50 mg/kg included minimal to moderate decreases in red cell mass (decrease of RBC to 81% and to 74% of the pre-dose value, in males in females, respectively), decreased white blood cell counts primarily attributed to decreases in NEUT (to 20% of the pre-dose value, in both sexes) and PLT (to 66% of the pre-dose value, in females), and minimal to moderate increases in red cell distribution width.

PSB202 administration at ≥ 10 mg/kg resulted in a nearly complete depletion in B lymphocytes and nearly undetectable NK cells at 24 hr following the 1st dose, in a dose-independent manner. B cell counts in the 10 mg/kg dose group started to recover on Day 29 and returned to near or above baseline on Day 85. Whereas the reductions in the 200 mg/kg dose group were generally sustained until Day 85.

No detectable increase in cytokine production (IL-1β, IL-2, IFN-γ, and TNF-α) were noted. PSB202-related increases in MCP-1 and IL-6 concentrations were observed at 1-hour postdose after the first dose, with some additional increases noted after repeat PSB202 dosing on Day 29. Major microscopic findings included but were not limited to PBS202-related decrease in germinal centers in multiple lymph nodes and the spleen at doses ≥ 10 mg/kg, as a result of the direct pharmacological effect of the test article. Additionally, individual animals in all groups administered PBS202 had kidney and liver related histologic findings suggestive of ADA formation. However, in the 200 mg/kg group, the above histology findings noted at terminal euthanasia were not observed at recovery euthanasia, while PBS202-related decrease in germinal centers was partially recovered.

For additional details please refer to Sections 4.4.1 and 4.4.2 of the IB.

The NOAEL was determined to be 50 mg/kg. This dose level corresponds to Cmax values of 532 and 530 μg/mL, and AUC values of 33200 and 34900 μg*hr/mL, in males and females, respectively for PSB102, and Cmax values of 303 and 233 μg/mL, and AUC values of 20600 and 13700 μg*hr/mL, in males and females, respectively, for PSB107, on Day 22.

1.2.3 Determination of Recommended Starting Dose

Considering the totality of the nonclinical data, especially the efficacy and safety of PSB202, a First-in-Human (FIH) starting dose of QW **0.2 mg/kg (12 mg,** for a 60 kg

patient, administered as a flat dose) *i.v.* is proposed. This dose was calculated based on: the NOAEL that was obtained from the repeat dose toxicity study, the cytokine release assay, pharmacodynamic studies, and are in-line with known approved in-class dose ranges. The rationale for the proposed FIH starting dose of QW **0.2 mg/kg** is based on the evaluation of all available PSB202 preclinical pharmacology, PK, and toxicology data.

- Safety window: The NOAEL of 50 mg/kg via *i.v.* infusion was determined in the repeat-dose toxicology study (4-week, QW, *i.v.*) in cynomolgus monkeys. The human equivalent dose (HED) of NOAEL is 50 mg/kg calculated on body weight as the molecular weight of PSB202 is > 100 KDa. Therefore, after applying a 6-fold safety factor, the maximal recommended starting dose (MRSD) is 8.3 mg/kg. A dose of **0.2 mg/kg** QW, provides for a ~42-fold additional safety margin relative to the MRSD.
- Cytokine release: PSB202 was shown to induce the release of TNFα and IL-6 in plate-bound form in the EC50 range of ~3.75 - ~4.74 μg/mL, for TNFα and IL-6, respectively. Very low levels of TNFα and IL-6 were also induced by soluble PSB202, but without dose relationship. These EC50 values correspond to possible C_{max} in a dose range of ~0.175 – 0.22 mg/kg of PSB202 (based on the human plasma volume of 2.8 L with a human body weight of 60 kg). The proposed PSB202 starting dose of **0.2 mg/kg** is within the reported range of TNFα and IL-6 release effect *in vitro,* and close monitoring of immune-related parameters might be warranted in the Phase I clinical study.
- Potential side-effects of same class: Though immune related effects in the animal study using humanized antibodies in a monkey are not predictive for the human, it is not uncommon to have related immune-mediated infusion reactions or ADA with antibody therapeutics for cancer and specifically B-cell malignancies in the clinic. For example, rituximab, a mouse-human chimera administered at 10 mg/kg (600 mg) QW, has been reported to have an overall incidence of infusion-related reaction in 77% (7% grades 3–4) of patients during the first infusion, 30% (2% grades 3–4) during the fourth infusion, and 14% (no grade 3–4 events) during the eighth infusion (Vogel, W.H. 2010). 37% of patients with relapsed or refractory NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 to obinutuzumab infusion (a humanized anti-CD20 monoclonal antibody), which is administered at 16.66 mg/kg (1000 mg) QW. In early phase clinical studies of anti-CD37 mAb, the toxicity profiles of otlertuzumab and BI 836826 appear to be similar to the anti-CD20 mAb, with the most common toxicities (mostly grade 1/2) being IRR, neutropenia, thrombocytopenia, fever, and fatigue (Byrd et al., 2014; Stilgenbauer et al., 2019). These immune reactions are generally addressed in the clinic (Vogel, W.H. 2010) and an awareness of them is

included in PSB202 Phase I studies. The proposed initial Phase I dose of PSB202 of 0.2 mg/kg, corresponding to a fixed (flat) dose of approximately 12 mg, is 50-fold and 83-fold lower than rituximab and Obinutuzumab clinical dosing, respectively.

The proposed starting dose in the clinical study for *i.v.* administration of PSB202 is **0.2 mg/kg** (12 mg/dose, for a 60 kg patient, administered as a flat dose) QW and is supported by the totality of the non-clinical data. This value is consistent with a considerable safety window and a dose consistent with an expected observable efficacy measured by B-cell depletion.

The starting dose of PSB202 for the proposed Phase 1/2 study was calculated according to the FDA's general guide for starting dose selection for investigational agents in cancer patients and ICH S9, after evaluation of all toxicity data. Dosing in the clinic will use fixed dosing in mg (as opposed to mg/m2) as there is no evidence that dosing by body surface area will reduce inter-subject variation.

1.3 Anticipated Risks

As PSB202 has not yet been administered to human subjects, potential risks, contraindications, and warnings are theoretical and are based on observations from animal testing.

1.3.1 Anticipated Risks from Animal Studies

Based on the nonclinical profile that includes results from animal toxicology studies, the theoretical risks of human exposure to PSB202 include the following:

In the 28 day repeat-dose toxicology study performed in cynomolgus monkeys, 3 animals were prematurely euthanized due to declining clinical condition that was attributed to immune-mediated infusion reactions, likely associated with ADA formation. It is common for ADA against human mAb to develop in animals, although ADA formation may also occur in humans. Immune-related reactions may be expected to occur with PSB202.

Other toxicities observed in nonclinical studies were mostly hematologic, including the expected depletion of B cells and NK cells, but also decreases in RBC mass and WBC counts. Consistent with the pharmacological effect of PSB202, in surviving animals target organ effects were observed at levels of ≥ 10 mg/kg and consisted of a decrease in germinal centers in multiple lymph nodes and the spleen and, as the adaptive response increased, secondary bone marrow cellularity and extramedullary hematopoiesis was observed at levels of ≥ 50 mg/kg. Hematologic parameters will be monitored throughout the clinical study. PSB202 induced detectable levels of MCP-1 and IL-6 in vivo and the release of TNFα and IL-6 in vitro, the latter at concentrations near the recommended first-in-human

starting dose; Investigators should monitor patients for signs and symptoms of cytokine release syndrome.

See the IB for further details of PK, PD, and toxicology nonclinical studies.

1.3.2 Safety Experience with Related Molecules

Rituximab (R) and obinituzumab (O) are marketed CD20+ targeted antibodies with known safety profiles. Of note, the clinical AE profiles associated with marketed CD20+ targeted antibodies may be due to both on target and off target effects. Examples of other therapeutic CD20+ targeted agents may have previously received are listed in Appendix B. Commonly occurring adverse events as well as serious, less common AE observed in patients receiving treatment with CD20+ directed antibody therapy include:

- Infusion reactions (chills, rigors, transient fever; grade 3 and 4 IRR may be observed)
- Hypersensitivity/serum sickness
- Hemorrhage
- Infections, including serious bacterial, fungal and viral infections
- Hepatitis B virus reactivation, including fulminant hepatitis
- Cytopenias, including grade 3-4 neutropenia and thrombocytopenia
- Hypertension
- Tumor lysis syndrome
- Progressive multifocal leukoencephalopathy, rare, but potentially fatal

Anti-CD37 targeting mAb (otlertuzumab and BI 836826) have been tested as monotherapy and in combination with bendamustine in early phase clinical studies of CLL and indolent NHL (Byrd et al., 2014; Stilgenbauer et al., 2019). The overall safety profile of these drugs overlaps with anti-CD20 mAb with most AE being grade 1 or 2. The most commonly observed grade 3/4 AEs included neutropenia, thrombocytopenia, fatigue, fever, and IRR. Toxicity of regimens combining anti-CD37 with bendamustine was comparable to the BR (bendamustine plus rituximab) regimen (Robak et al., 2016). Overall, anti-CD37 mAb appear to be safe and well tolerated.

1.4 Benefit/Risk

Three CD20+ targeting monoclonal antibodies (rituximab, obinutuzumab, ofatumumab) are currently marketed in the USA for the treament of certain B-cell malignancies. No CD37+ targeted therapy is currently in approved, although early phase clinical studies have demonstrated promising efficacy of the anti-CD37 mAbs otlertuzumab and BI 836826 in

treating CLL, NHL, and WM, both alone and in combination with bendamustine (Byrd et al., 2014; Stilgenbauer et al., 2019; Robak et al., 2016). Concurrent targeting of CD37+, often co-expressed in the same malignancies, may overcome resistance to CD20+ single target antibodies.

When viewed as a whole, these and following considerations indicate the benefit/risk ratio for PSB202 in this study is favorable. Patients with CD20+ / CD37+ expressing malignancies (CLL, WM, MCL, MZL and other NHLs) who have failed rituximab and/or obinutuzumab-containing regimens due to acquired resistance or treatment intolerance represent populations with high unmet need. As discussed in Section 1.1, available therapies for these patients provide short-term palliation (i.e., idelalisib, chemotherapy, BTK-inhibitors, BCL2 inhibitors (i.e., venetoclax), second generation anti-CD20+ monoclonal antibody therapy) or have the potential to be very toxic (i.e., autologous stem cell transplant, CAR-T). Therefore, there is an urgent need to identify new targeted therapies that target CD20+ and CD37+ via alternate routes.

Because PSB202 is an experimental medicine, it is possible that unforeseen, unknown or unanticipated adverse events and toxicities may occur. However, as detailed below, this clinical protocol is designed to mitigate risks to patients through a detailed plan for cautious dose escalation, careful safety monitoring, systematic review of AEs, serious adverse events (SAEs), and PK, and active pharmacovigilance review to assess for safety signals or trends. This Phase 1a/1b study of PSB202 is designed to understand the safety, PK, maximum tolerated dose (MTD) and anti-tumor activity of PSB202 in patients with relapsed/refractory B cell malignancies.

2 STUDY OBJECTIVES

2.1 Primary Objective (Phase 1a)

To determine the maximum tolerated dose (MTD)/recommended Phase 1b dose (RP1bD) of PSB202 by *i.v.* injection in patients with CLL/SLL, indolents B-cell NHL(B-NHL), and WM who have failed or are intolerant to standard of care.

2.2 Secondary Objectives (Phase 1a)

- To determine the safety profile and tolerability of PSB202 including acute and chronic toxicities, and presence or absence of treatment-emergent ADA.
- To characterize the PK and pharmacodynamic (PD) properties of PSB202.
- To assess the preliminary anti-tumor activity of PSB202 based on overall response rate (ORR) according to International Workshop Guidelines for CLL/SLL (IWCLL 2018, (Hallek, Cheson et al. 2018)) and WM (IWWM8, (Leblond, Kastritis et al. 2016), Lugano Treatment Response Criteria for Mantle Cell Lymphoma (MCL), MZL and other NHL (Lugano 2014, (Cheson, Fisher et al. 2014)), or other criteria as appropriate to tumor type, as assessed by the Investigator.

2.3 Primary Objective (Phase 1b)

To assess evidence of anti-tumor activity of PSB202 based on ORR as assessed by the Investigator, in guidance of and following protocol-referenced international standards. An independent review committee (IRC) may review the Investigators' assessments.

2.4 Secondary Objectives (Phase 1b)

- To assess, for each phase 1b cohort, the preliminary anti-tumor activity of PSB202 by determining:

  ORR as assessed by Central Review for this secondary objective

  Best overall response (BOR) as assessed by the Investigator

  Duration of response (DOR) as assessed by the Investigator

  Progression-free survival (PFS) as assessed by the Investigator and Central Review

- To determine the safety profile and tolerability of PSB202, including treatment-emergent ADA.
- To characterize the PK/PD properties to produce evidence of biological impact for PSB202.

2.5 Exploratory Objectives (Phase 1a)

- To determine the relationship between PK and drug effects, including efficacy and

safety.

2.6 Exploratory Objectives (Phase 1a and Phase 1b)

- In CLL/SLL patients with a clinical CR, evaluate minimal residual disease (MRD), assessed in the peripheral blood and/or bone marrow, by molecular assays including next-generation sequencing (NGS), allele-specific oligonucleotide polymerase chain reaction (PCR) and/or flow cytometry, as per institutional standard of care.
- In FL patients: in responding patients, to characterize reversion of peripheral blood *BCL-2* rearrangement.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is an open-label, multi-center Phase 1a/1b study of PSB202 by *i.v.* infusion in patients with indolent B cell NHL (including CLL/SLL, FL1-3a, MZL/MALT, WM and MCL-indolent subtype) who have failed or are intolerant to standard of care and require systemic therapy based on disease-specific criteria (See Appendices C, D, E).

This study includes 2 parts: phase 1a (dose escalation) and phase 1b (dose expansion).

In phase 1a, patients will be enrolled using an accelerated titration design in the first 3 dose (likely sub-therapeutic) levels, with a standard 3+3 design thereafter. Previous studies with CD20+ targeted agents indicate that significant (e.g., 90% or greater) CD20 target engagement in patients is required for clinical efficacy (Byrd, Furman et al. 2013, Woyach, Furman et al. 2014, Tam, Grigg et al. 2015). Hence 3 study drug administrations are provided in Cycle 1 (C1, Day 1, Day 8 and Day 15) as loading dose, and then on Day 1 of Cycle 2-9. The starting dose of PSB202 in *i.v.* administration is 12 mg. The first PSB202 dose will be administered over an infusion duration of 4 hours. Absent Grade 2 or worse infusion related reaction (IRR) during initial dosing, infusion speed may be increased gradually (i.e. 30-45 minutes incremental infusion time reductions) during subsequent infusions, but never to an infusion time of less than 120 minutes for the target dose. Dosing will be fixed as total milligram (mg; as opposed to weight or BSA-based). The DLT period will be 28 days, commencing with the first dose of PSB202. Cycle length will be 21 days. Hence the DLT period includes the full first cycle and up to the first 7 days of follow-up of the second cycle if the C2, D1 dose is given per the protocol-directed schedule.

The determination of the PSB202 dose for the Phase 1b portion of the study will take into account the entirety of PK, PD, efficacy and safety data. Once the MTD and/or RP1bD is identified, patients will be enrolled to one of three phase 1b dose expansion cohorts depending on tumor histology, tumor genotype, and prior treatment history.

Phase 1a and phase1b will enroll patients with histologically confirmed (by local pathology) previously treated indolent BNHL who meet eligibility criteria as applicable (refer to Section 4).

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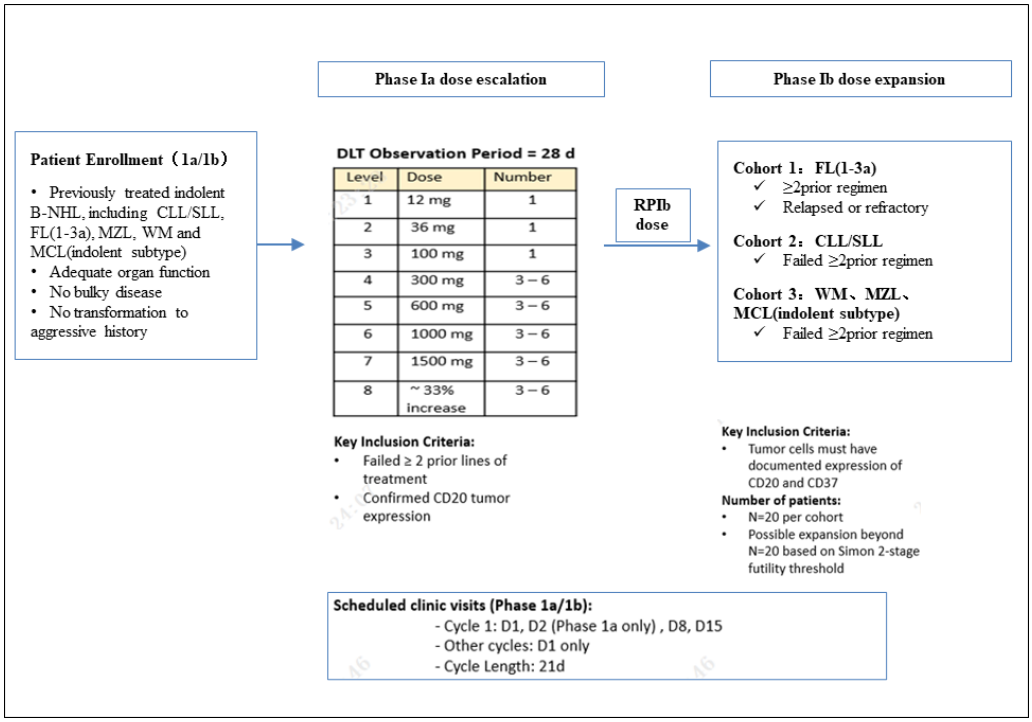
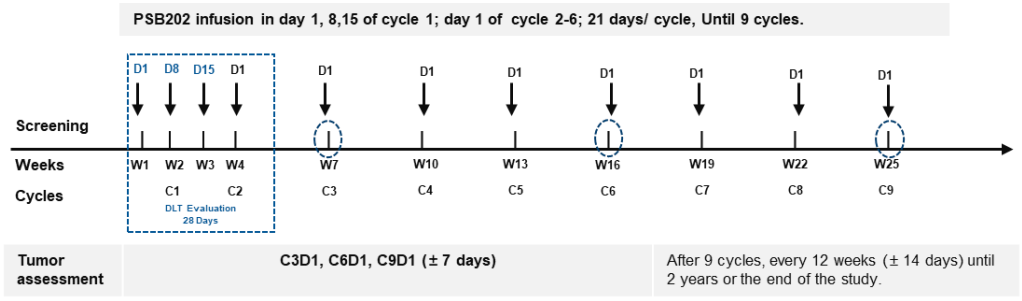
Figure 1 Study Schema





3.2 General Treatment Procedures

Patients will receive the assigned PSB202 dose on Cycle 1 Day 1 (C1D1) in accordance with the cohort assignment. The starting dose of PSB202 is 12 mg administered by *i.v.* infusion. An additional loading dose will be provided on C1D8 and C1D15, PSB202 will be administered only on Day 1 of subsequent cycles. In phase 1a and phase 1b, cycle length is 21 days. The DLT evaluation period during phase 1a comprises 28 days, i.e. the DLT-period extends into Cycle 2 to include the C2D1 dose with 7 days of C2 follow-up.

Individual patients will continue PSB202 dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation, as outlined in Section 6.4.

Both phase 1a and phase 1b will consist of a screening period, a treatment period, an End of Treatment (EOT) visit, a Safety Follow-up (SFU) visit, and Long-Term Follow-up (LTFU) of up to two years from any subjects start of study date.

All treated patients will undergo an SFU visit that will be conducted within 3 weeks (+14 days) of last dose of study drug.

After treatment discontinuation, all patients will enter the LTFU period of the study. Patients who discontinue study treatment for reasons other than PD, withdrawal of consent, or initiation of a new anticancer therapy(ies), will also be assessed for progression of disease during LTFU until PD, withdrawal of consent, or initiation of a new anticancer therapy(ies). Once PD is confirmed, patients will be followed for survival status by telephone.

3.3 Phase 1a and Maximum Tolerated Dose Determination

Phase 1a will enroll patients with histologically confirmed indolent B-NHL (including CLL/SLL, FL1-3a, MZL/MALT, WM and MCL-indolent subtype) who have failed or are intolerant to standard of care as described in Appendix B.

Dose escalation will follow an accelerated titration design with single-patient dosing in the first three cohorts. The occurrence of ≥1 Grade 2 or higher AE in any of the single-patient cohorts during the first cycle of study drug, that cannot be reasonably attributed to the patient's underlying disease, other medical condition or concomitant medications, will result in a switch to a 3+3 dose escalation regime for the current and subsequent dose levels. It is hoped that accelerated titration design will minimize the number of patients exposed to subtherapeutic doses of PSB202 and hasten the identification of a safe and therapeutic dose.

The starting dose of PSB202 is 12 mg *i.v.*. The DLT period will be 28 days, commencing with the first dose of PSB202. Cycle length will be 21 days.

Dose escalations will be ~3 times the previous dose level for the first 3 dose escalations. After the third dose increase, a modified Fibonacci dose escalation will be used to guide subsequent dose escalation, with planned increments of 100%, ~67%, ~50%, and then ~33% for further dose escalations. In addition, the Safety Review Committee (SRC) may modify the actual dose escalated to or the dosing schedule may be changed (e.g. step-up dosing with lower "priming doses", upon review of available PK, safety and efficacy data. Other than dose escalations from the lowest (likely sub-therapeutic) dose-levels, no individual dose escalation will be more than twice the total daily dose of the prior level.

Planned dose levels for PSB202 in the study phase 1 are outlined in **Table 2**.

Table 2 Planned Dose Levels for PSB202

Level	Dose	Frequency
1 (starting dose)	12mg	D1, D8, and D15 of Cycle 1 (loading doses), then D1 of each subsequent cycle (21-day cycles)
2	36 mg	
3	100 mg	
4	300 mg	
5	600 mg	
6	1000 mg	
7	1500 mg	
8 and higher	~ 33% increase	

Dosing above 2500 mg is not planned in this study. For clinics preferring an oral pre-medication regimen, an oral steroid (i.e. prednisone) and/or montelukast are recommended to be added to the pre-medication regimen during Cycle 1 as per institutional pre-medication standard of care for other CD20+ targeted monoclonal anti-bodies (i.e. obinituzumab). Standard pre-infusion medications (650-1000 mg acetaminophen and anti-histamine) will be provided 30-60 minutes prior to study drug infusion., For clinics preferring an IV premedication regimen, glucocorticoid (10-20 mg dexamethasone or 40-80 mg methylprednisolone or equivalent other steroid) is recommended be provided prior to PSB202 infusions. . Patients deemed at increased risk for tumor lysis syndrome (high tumor burden, absolute lymphocyte count $\geq 25 \times 10^9$/L will be provided with anti-hyperuricemics (e.g. allopurinol or rasburicase) pre-infusion. PEPCID (Famotidine) may be added per investigator discretion.

A meeting of the SRC will be convened for each phase 1a dose escalation decision (except for accelerated dose titration cohort). Each patient in each cohort must have completed safety assessments through the first 28 days of treatment and must have received a minimum of 75% of the planned total dose during that time (e.g., 3 of the 4 weekly doses that comprise Cycle 1 and C2D1), to be eligible for the assessment of a DLT. Patients who

receive less than 75% of planned doses due to reasons other than a DLT will be replaced for the determination of the MTD but will remain part of the safety population if they receive at least 1 dose of study drug. Any toxicity resulting in treatment with less than 75% of planned doses will be reviewed by the SRC and will be considered a DLT if the SRC determines the toxicity cannot be attributed to the patient's underlying disease, other medical condition or concomitant medications.

One to 6 patients in each cohort must have completed 28 days of safety assessment in Cycle 1 without a DLT, and the DLT rate must be < 33% (i.e., 0 of 1, 0 of 3, or 1 of 6 patients), before the next cohort initiates accrual. In addition, guided by review of all safety data including any safety signals emerging during treatment beyond the period, SRC may determine that additional patients should be evaluated at an intermediate dose level lower than the highest dose reached during escalation. Alternative dosing schedules such as step-up dosing or priming dose may also be recommended for evaluation within the 3+3 framework. As guided by emerging safety data, the SRC may specify step-up dosing, with one or more lower priming doses of PSB202 at C1D1 and/ or C1D8. Escalation will proceed through all dose levels or until the Sponsor and SRC determine that a suitable dose has been achieved based on available data (PK, safety, and clinical activity).

During Phase 1a, after completion of the 28-day DLT period, intra-patient dose escalation may be permitted by the Sponsor, provided that the patient is tolerating their current dose with no ≥ Grade 2 AE, and the dose level to which the patient will be escalated has a DLT rate <33% and has been declared safe by the SRC.

During phase 1a, at the discretion of the Sponsor, dose levels previously declared safe by the SRC may be expanded by an additional ~5 "backfill" patients to further investigate the tolerability, PK, and biological activity of PSB202. Enrollment of patients to the open dose escalation cohorts will take precedent. The SRC will continue to monitor the cumulative safety data from the cohorts previously declared safe and the current dose cohort under evaluation.

A recommended Phase 1b/Phase 2 dose will be confirmed independently for CLL- versus non-CLL patients. Prior to opening the Phase 1b expansion cohorts and/or Phase 2 studies, the Phase 1a dose level that suggests the MTD or recommended Phase 1b dose may be expanded with additional patients up until such time that a minimum of 6 CLL/SLL *and* 6 non-CLL patients have been treated. The opening of CLL- and non-CLL expansion cohorts may proceed along independent timelines once a recommended Ph1b dose is confirmed, guided by safety data from at least 6 DLT-evaluable patients of corresponding histology showing a DLT rate of < 33% at the proposed dose level. Dose de-escalation is possible if one disease histology exhibits a markedly different safety profile versus the other histology. This approach allows for the possibility that a different MTD and hence a different Phase 2 or Phase 1b dose is characterized and selected for CLL- versus non-CLL expansion cohorts.

3.3.1 Dose-limiting Toxicity (DLT) Definition

A DLT is defined as any of the treatment-emergent adverse events (TEAEs; a TEAE is defined as an AE that starts on or after the first dose of study drug) listed below, as defined by the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5 (NCI CTCAE v5), and for hematologic adverse events in CLL patients, IWCLL criteria for hematologic toxicity (Hallek, Cheson et al. 2018), occurring during the first 28 days of study drug, and the AE is not reasonably attributed to the patient's underlying disease, other medical condition or concomitant medications. The DLT definitions are:

1) Any ≥ Grade 3 non-hematologic toxicity **except for**:
   - Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT) gamma-glutamyl transferase (GGT) and/or total bilirubin elevation. However, any combination of laboratory and clinical findings consistent with Hy's Law criteria for drug-induced liver injury will always be considered a DLT.
   - First occurrence of Grade 3 electrolyte abnormalities and/or creatinine clearance decrease resolving to Grade 2 (or baseline if baseline is ≥ Grade 2) within 48 hours with supportive treatment.
   - Grade 3 infusion reaction (rigors, chills, muscle spasms etc.) resolved within 24 hours of onset.
   - Grade 3 fatigue, nausea, vomiting, or diarrhea as long as it does not necessitate hospitalization, TPN, or tube feeding.
   - Grade 3 infection responding to appropriate antibiotic/anti-viral therapy.
   - Any Grade 3-4 asymptomatic laboratory abnormality that is not clinically significant and does not require therapeutic intervention
2) Any ≥ Grade 3 hematologic toxicity will be considered a DLT **except for**:
   - Grade 3 neutropenia without fever
   - Neutropenic fever resolved within 48 hours with appropriate antibiotic- and medical management
   - Grade 4 neutropenia without fever lasting 10 days or less
   - Grade 3/4 thrombocytopenia that does not result in bleeding. Grade 4 thrombocytopenia lasting ≥7 days is a DLT.
   - Grade 3/4 lymphopenia/lymphocytosis
   - Grade 3/4 white blood cell (WBC) decreased
3) Grade 5 (fatal) toxicity
4) Grade 3 or 4 cytokine release syndrome
5) Any toxicity, regardless of the NCI CTCAE v5.0 grade, resulting in discontinuation, dose reduction or treatment with less than 75% of planned doses (i.e., receipt of less

than 3 of 4 doses planned during the DLT-period), will be reviewed by the SRC, and will be considered a DLT if the SRC determines the toxicity cannot be attributed to the patient's underlying disease, other medical condition or concomitant medications.

3.4 Phase 1b

Once the MTD or RP1bD is identified, ~20 patients with CLL/SLL, various indolent NHL histologies, or WM will be enrolled to one of three phase 1b dose expansion cohorts (determined locally).

Cohorts 1 through 3:

- Cohort 1: FL1-3a, progressed during or within 6 months after at least two prior regimens, at least one of which contained anti-CD20 antibody (i.e. single-agent R or R-chemo)
- Cohort 2: CLL/SLL failed and progressed after two or more prior lines of therapy.
- Cohort 3: WM, MZL, MCL (indolent subtype) failed at least 2 prior regimens. MCL-patients must have received an alkylating agent.

Cohort expansion is conditioned on patients initially enrolled in the cohort to have shown a response rate higher than the pre-specified futility proportion (See Section 8.3).

In Phase 1a and 1b, all patients should have documented CD20+ expression based on previous pathological reports prior to dosing. In Phase 1a, CD37+ expression will be recorded in the CRF if available in the patient chart, but will not be required if not available. For Phase 1b, archival reports and/or material may be used for documentation of CD37+ status, but in case no archival CD37+ result or library specimen is available, new sampling will be performed pre-dosing, and should be evaluated for CD20 and CD37 by a laboratory with certification by Clinical Laboratory Improvement Association (CLIA), International Organization for Standardization/Independent Ethics Committee (ISO/IEC), College of American Pathologists (CAP), or equivalent. Dosing need not await reporting of the result of confirmatory CD37+ testing. Hence, confirmation of CD37+ is optional, but CD20+ positivity is always required. The Sponsor or Sponsor designee should be contacted to confirm test results to ensure trial eligibility. Refer to Appendix A and Appendix B for examples of CD20+ monoclonal antibodies, BTK inhibitors and examples of intolerance, refractory disease and relapsed disease.

PSB202 will be administered to the phase 1b patients at the MTD or RP1bD. In addition, the dose (and schedule) chosen for phase 1b may be changed by the SRC based on emerging data (e.g., PK, safety, and/or efficacy) as long as the new dose is not greater than the highest dose that has a DLT < 33% and is determined to be safe by the SRC in phase 1. If the RP1bD is changed based on emerging data, patients enrolled to phase 1b at a different dose may have the dose changed to the new dose. If a new dose level or dosing

schedule is selected at Phase 1b commencement or during Phase 1b, the protocol will be amended.

Patients treated during dose escalation (Phase 1a) at the MTD/RP1bD who also meet the criteria for one of the Phase 1b cohorts may be considered as part of the evaluable patients for that cohort for tumor/lymphoma response.

A statistical justification for cohort size is discussed in Section 8.3.

3.5 Number of Patients

Including backfill patients, in Phase 1a of the study, it is anticipated that ~32-40 patients will be enrolled to define the MTD (or RP1bD) of PSB202. The actual number of patients enrolled is dependent on the number of patients enrolled in each dose escalation cohort, the number of cohorts enrolled, the number of additional patients enrolled to dose levels previously determined to be safe and when DLTs occur. During phase 1b, up to 20 patients may be enrolled in each of 3 cohorts. Therefore, ~92-100 patients may be enrolled in the study.

4 SELECTION OF STUDY POPULATION

Potential patients age 18 years and older must sign an informed consent form (ICF) before any study-specific screening tests are conducted.

4.1 Inclusion Criteria

For Phase 1a -Dose Escalation:

1. Histologically confirmed CD20+ expressing indolent B-cell NHL (defined below), CLL or WM, failed and/or progressed or intolerant to at least 2 standard-of-care therapies;
2. Relapsed/refractory following at least 2 prior lines of treatment. Prior treatment received must be documented on the enrolment form. In FL patients, at least 1 line of treatment must have contained rituximab. Examples of qualifying prior treatments are provided in APPENDIX A; this is not intended to be an exhaustive list, as local standards of care may vary. Relapse and refractory are defined in APPENDIX B.
3. First 3 dose-levels only: in the opinion of the investigator, able to tolerate a potentially subtherapeutic dose of PSB202 for the duration of a 28-day DLT observation window.

For Phase 1b – Dose Expansion:

4. Histologically confirmed CD20+ expression. Documentation of CD37+ status, if unavailable at screening, CD37+ expression may be confirmed from new or archived blood specimens after enrollment.
5. Indolent NHL: histologies that may be included are CLL/SLL, MZL, FL, MCL or WM failed, relapsed/refractory or intolerant to at least 2 standard of care therapies.
6. Patients must have documented disease progression after at least two prior standard-of-care regimens.

All Patients:

7. Signed Informed Consent;
8. Eastern Cooperative Oncology Group (ECOG) 0-2
9. Last dose of any anti-CD20 antibody therapy must have been >4 weeks before the first dose of PSB202
10. Patients with a medical history of Covid-19 positivity at any time prior to enrollment, must be retested within 7 days of enrollment and confirm Covid-19 negativity by a PCR-test.
11. At least 18 years of age. There is no upper age restriction.
12. Patients must have measurable disease (excepted CLL and WM).
13. Four weeks wash-out from any other prior cancer therapy, including rituximab and BTK-inhibitors. However, some heavily pretreated patients are at risk for significant morbidity from accelerated disease progression or “flare” when treatment is discontinued prior to the initiation of subsequent effective therapy. Absent residual

toxicity and with documented Medical Monitor approval, such patients may receive study drug after five drug half-lives have passed following discontinuation of the immediate pre-study therapy.

14. Adequate hematologic and coagulation status, defined as the following on C1D1 before treatment:
    - Absolute neutrophil count (ANC) ≥ 0.75× 10^9/L and not requiring growth factors;
    - Platelet count ≥ 75 × 10^9/L not requiring transfusion support; if there is documented bone marrow involvement, platelet transfusions may be used up to 7 days prior to C1D1 to achieve this threshold.
    - Hemoglobin (Hb) ≥ 9g/dL (90g/L) not requiring transfusion support or growth factors.
    - Adequate coagulation, defined as aPTT and PT (or INR) not greater than 1.5 × upper limit of normal (ULN) (patients appropriately anticoagulated for a preexisting medical condition [e.g., atrial fibrillation] may be eligible with documented Sponsor approval).
15. Adequate hepatic and renal function, defined as:
    - ALT or AST ≤2.5 × the ULN or ≤ 5 × ULN with documented liver involvement.
    - Total bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN with documented liver involvement and/or Gilbert's Disease Adequate renal function.
    - With expected creatinine clearance (Ccr, equation as below) or estimated glomerular filtration rate (eGRR) via Cockcroft-Gault equation ≥50 mL/minute.

    $$\text{Ccr} = \frac{(140-\text{Age}) \times (\text{Weight/kg}) \times 0.85 (\text{if female})}{72 \times \text{serum creatinine (mg/dl)}}$$

    Or

    $$\text{Ccr} = \frac{(140-\text{Age}) \times (\text{Weight/kg}) \times 0.85 (\text{if female})}{0.818 \times \text{serum creatinine } (\mu\text{mol/L})}$$

16. Ability to comply with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
17. Willingness of men and women of reproductive potential to observe conventional and effective birth control for the duration of treatment and for 3 months following the last dose of study treatment; this may include barrier methods such as condom or diaphragm with spermicidal gel.

4.2 Exclusion Criteria for Phase 1a and Phase 1b

Phase 1a (dose escalation) only:

1. NHL with bulky disease
   defined as mass ≥ 10 cm in longest diameter (LDi)

2. Transformation (e.g., Richter's transformation, prolymphocytic leukemia, transformed NHL, blastoid lymphoma) prior to planned start of PSB202. In addition, no concurrent investigational therapy is permitted.

All patients: 1a (dose escalation) and Phase 1b (expansion):

3. Major surgery within 4 weeks prior to planned start of PSB202
4. Radiotherapy with a limited field of radiation for palliation within 7 days of the first dose of study treatment, except for patients receiving radiation to more than 30% of the bone marrow or receiving whole brain radiotherapy, which must be completed at least 4 weeks prior to the first dose of study treatment
5. Continuation of certain standard of care anticancer therapies, including hormonal therapy for breast and prostate cancer, is allowed, provided they are not on the list of prohibited concomitant medications.
6. Any unresolved toxicities from prior therapy greater than CTCAE (version 5.0) Grade 2 or greater at the time of starting study treatment except for alopecia.
7. History of autologous stem cell transplant (auto-SCT) or chimeric antigen receptor-modified T-cell (CAR-T) therapy within the past 180 days with any of the following: cytopenias from incomplete blood cell count recovery post-transplant, need for anti-cytokine therapy, residual symptoms of neurotoxicity > Grade 1, or ongoing immunosuppressive therapy.
8. Active graft versus host disease (GVHD, including rejection resultant from any prior solid organ transplants, if received), cytopenias from incomplete blood cell count recovery post-transplant, need for anti-cytokine therapy, residual symptoms of neurotoxicity > Grade 1, or ongoing immunosuppressive therapy.
9. History of allogeneic stem cell transplant (allo-SCT) or allogeneic CAR-T at any time in the patient's medical history
10. Known central nervous system (CNS) involvement by lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable and without evidence of active CNS-disease may be eligible if a clinical rationale is provided by the Investigator and with documented Sponsor approval.
11. Active auto-immune cytopenia (e.g., autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP])

12. Cerebrovascular accident (CVA), Transient ischemic attack (TIA), myocardial infarction, unstable angina, or New York Heart Association (NYHA) class III or IV heart failure < 6 months of study screening; mean ECG QT-interval corrected according to Fridericia's formula (QTcF) > 450 milliseconds (ms) (males) or > 470 ms (females) obtained from three ECGs; uncontrolled arrhythmia < 3 months of study screening. Patients with rate-controlled arrhythmias may be eligible for study entry at discretion of the Investigator.
13. Active uncontrolled systemic bacterial, viral, fungal or parasitic infection (except for fungal nail infection), or other clinically significant active disease process which in the opinion of the Investigator and the Sponsor makes it undesirable for the patient to participate in the trial. Screening for chronic conditions is not required.
14. Tested positive for Human Immunodeficiency Virus (HIV) is excluded (due to potential drug-drug interactions between anti-retroviral medications and PSB202 and risk of opportunistic infections). For patients with unknown HIV status, HIV testing will be performed at Screening.
15. Active viral hepatitis (B or C, HBsAg, anti-HBs/HBcAb and anti-HCV Ab tests) as demonstrated by positive serology or requiring treatment. Subject who are anti-HBs/HBcAb (+) without detectable HBV-DNA are eligible. Subjects with a history of Hepatitis C and have received successful curative treatment are eligible.
16. Pregnancy or lactation.
17. Active autoimmune disease or history of autoimmune disease requiring systemic therapy < 2 years prior to screening except hypothyroidism, vitiligo, Grave’s disease, Hashimoto’s disease, or Type I diabetes. Patients with childhood asthma or atopy that has not been active in the 2 years prior to study screening are eligible.
18. History of drug-induced liver injury or cirrhosis
19. History of drug-related pneumonitis or interstitial lung disease
20. Patients with significant medical diseases or conditions, as assessed by the Investigator and Sponsor, that would substantially increase the risk-benefit ratio of participating in the study. Active second malignancy unless in remission and with life expectancy > 2 years.

5 ENROLLMENT PROCEDURES

A representative from the investigational site will contact the Sponsor or designee when a potential study candidate is identified and a patient number (which will consist of a 3-digit site number followed by a sequential accession number) will be assigned that will be used throughout both Screening and study participation. Once screening procedures have been completed for the patient, a completed enrollment form will be submitted to the Sponsor or designee to confirm eligibility.

Patients who are determined to be screen failures can be re-screened. Re-screened patients will be provided a new patient number.

The enrollment form will be returned to the site with the cohort assignment (if applicable) and must be received by the site before treatment may commence. Refer to the Study Manual for enrollment form, contact numbers, and other details of enrollment.

6 TREATMENT

6.1 Investigational Product

PSB202 will be provided in 15 mL vials for *i.v.* administration. Each vial is filled to 8 mL and contains 200 mg PSB202.

6.1.1 Vials

The site pharmacist will dispense vials to the infusion unit in an amount necessary to allow for outpatient administration at the assigned dose level. Dosing is intended to be fixed (i.e., not weight-based or BSA-based).

Vials are to be stored between 2 ℃ and 8 ℃.

6.2 PSB202 Administration

6.2.1 General Dosing Instructions

Section 3.3 and Section 3.4 provide a description of dosing during phase 1a and phase 1b, example dose levels for phase 1 are indicated in **Table 2**. Dosing during phase 1b will be at the MTD/RP1bD. In phase 1a and phase 1b, cycle length will be 21 days.

At the designated dose level/assigned cohort, the initial dose will be administered over 4 hrs. Absent grade 2 or worse infusion reactions, the infusion duration may be reduced, step-wise in 30-45 minute increments, to a shorten the duration, but never to less than 120 minutes for the full dose. Absent Grade 2 or worse IRR at the first dose, infusion time at the second (C1D8) infusion is 3 hrs.15 min, etc. If the dosing schedule changes, these time windows may be adjusted accordingly.

Patients will continue PSB202 dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation.

6.2.2 Cycle 1: Phase 1a and Phase 1b

Patients will begin dosing on C1D1 according to their assigned cohort. Serial blood samples for PK monitoring will be collected and the patient will be monitored for safety as outlined in Section 7.2. Cycle length is 21 days during both phase 1a and phase 1b; the DLT treatment/observation period during phase 1a will be 28 days: Days 1 to 21 of Cycle 1 and Days 1 to 7 of Cycle 2.

6.2.3 Cycles 2 and Higher: Phase 1a and Phase 1b

In accordance with the assigned dose level (or for phase 1b, the RP1bD), each patient will receive PSB202 in 21-day cycles until PD, unacceptable toxicity, or other reasons for treatment discontinuation.

6.2.4 Dose Delays/Modifications

Cycles are 21 days since receiving the first dose of study drug regardless of whether treatment interruption, disease assessments should continue to follow the original schedule.

Toxicities such as nausea, vomiting, or diarrhea, or dizziness or dehydration related to these symptoms, may be managed with increased supportive care, including hydration, electrolyte repletion, and the use of anti-emetics such as serotonin type 3 (5-HT3) antagonists and/or anti-diarrheal medications such as loperamide as appropriate.

6.2.4.1 Phase 1a, Cycle 1

Dose reductions are not permitted during the DLT evaluation period. A delay in dosing of no more than one of the four doses during the DLT-period for reasons other than Grade 2 or worse toxicity does not compromise DLT evaluability of a given subject.

A patient who experiences a DLT is withdrawn from study, i.e. not restarted at a lower dose.

A patient with dose interruption/delay or a missed dose for reasons other than DLT may restart therapy if it is considered in his/her best interest to resume/continue therapy and with Sponsor approval. Upon restarting, such a patient may have the dose reduced by 1 dose level (**Table 4**). If the patient requires a dose delay of > 21 days, the patient will have treatment permanently discontinued.

6.2.4.2 Phase 1a Cycles 2 and Beyond and Phase 1b All Cycles

Table 3. Dose modifications for Phase 1a Cycle 2 and beyond and Phase 1b all cycles

Worst toxicity CTCAE V5.0 Grade	**Recommended dose interruption, delay and discontinuation for PSB202 during a cycle of treatment**
Hematology	
Neutropenia	
Grade 3 (ANC < 1000-500/mm^3)	Dose delay until resolved to ≤ Grade 2 If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, lower 1 dose level
Grade 4 (ANC < 500/mm^3), Grade 3 neutropenic fever	Dose delay until ≤ Grade 2 If resolved in ≤ 10 days, lower 1 dose level If resolved in > 10 days, then discontinue from PSB202 treatment.
Thrombocytopenia	
Grade 3 (PLT < 50,000 – 25, 000/mm^3)	Dose delay until resolved to ≤ Grade 2 If resolved in ≤ 7 days, then maintain dose level. If resolved in > 7 days, lower 1 dose level Discontinue PSB202 if Grade 3 > 21 days or associated with significant bleeding

Worst toxicity CTCAE V5.0 Grade	**Recommended dose interruption, delay and discontinuation for PSB202 during a cycle of treatment**
Grade 4 (PLT < 25,000/mm^3)	Dose delay until resolved to ≤ Grade 2 If resolved to ≤ Grade 2 in ≤ 7 days, then lower 1 dose level. If resolved in > 21 days, then discontinue from PSB202 treatment.
Non-hematology (modifications for IRR are described below)	
Grade 3 (except those correctable within 7 days and deemed by the investigator to be not clinically important)	Dose delay until resolved to ≤ Grade 1 or baseline. If resolved in ≤ 7 days, then maintain dose level. If resolved in >7 days but ≤ 14 days, then lower 1 dose level. If resolved in > 14 days, then discontinue from PSB202 treatment.
Grade 4 (life threatening)	Permanently discontinue PSB202 except for Grade 4 endocrinopathy or inflammatory arthritis.

If a patient experiences a Grade 2 or worse IRR despite pre-medication, infusion time for subsequent infusions may be increased with 30-45 minutes for subsequent infusions. Present Grade 2 or worse infusion reactions during/after prior PSB202 infusion, administration of 10-20 mg dexamethasone or equivalent 1 hr pre-infusion may be considered prior to subsequent infusions.

Patient with a *recurrent* grade 3 IRR despite adequate pre-medication they should not receive any more study drug.

All grade 4 IRR are off study.

A patient who experiences a clinically significant grade 3 or more AE (or more than 1 grade change from baseline if baseline is Grade 2 or above) ***may*** have PSB202 dosing held for up to 21 days to evaluate the AE and to allow for recovery (to Grade 1 or less or baseline if baseline is Grade 2 or above).

If the AE does not recover to Grade 1 or less, or baseline if baseline is Grade 2 within 21 days the patient will have treatment permanently discontinued, unless there is a compelling clinical rationale for additional dose reduction(s) articulated by the Investigator and approved by the Sponsor. Exceptions to this may be noted in Table 3. For each patient, a maximum of 2 dose reductions will be allowed. It is not allowed to increase the dose again after reducing the dose (Table 4).

Table 4 Suggested Toxicity Management during Phase 1a and Phase 1b

Dose Level	**Dose of PSB202**
Starting Dose	Dose level patient enrolled to

Dose Reduction	1a. Not allowed during DLT-period; after DLT period, see 1b rule. 1b. Reduce dose by not more than 1 dose level
Second Dose Reduction	Reduce dose by not more than 2 dose levels

All dose interruptions and dose modifications and the reasons for those changes will be recorded in the eCRF.

Table 5 Dose Modification for Hepatotoxicity

Adverse Reaction	Severity	Action and Dose Modification
Increased ALT/AST	Grade 2 • >3.0 - 5.0 × ULN if baseline was normal; • >3.0 - 5.0 × baseline if baseline was abnormal	• Close monitoring • Continue PSB202 at current dose level
	Grade 3 • >5.0 - 20.0 × ULN if baseline was normal; • >5.0 - 20.0 × baseline if baseline was abnormal	• Close monitoring • Withhold PSB202 until toxicity resolves to ≤ Grade 2, and restart PSB202 at dose reduced by one dose level • If no recovery to ≤ Grade 2 within 21d, discontinue permanently PSB202 and continue follow-up per protocol. • Permanently discontinue PSB202 for any recurrence of Grade 3 toxicity.
	Grade 4 • >20.0 × ULN if baseline was normal; • >20.0 × baseline if baseline was abnormal	• Close monitoring • Discontinue permanently PSB202
Blood bilirubin increased (Total bilirubin, TBL)	Grade 2 • >1.5 - 3.0 × ULN if baseline was normal; • >1.5 - 3.0 × baseline if baseline was abnormal	• Close monitoring • Withhold PSB202 until Grade ≤ 1 (total bilirubin level) or baseline • Continue treatment with PSB202 at current dose level
	Grade 3 • >3.0 - 10.0 × ULN if baseline was normal; • >3.0 - 10.0 × baseline if baseline was abnormal	• Close monitoring • Withhold PSB202 until Grade ≤ 1 (total bilirubin level) or baseline • Continue treatment with PSB202 at dose reduced by one dose level • If no recovery to ≤ Grade 1 within

Adverse Reaction	Severity	Action and Dose Modification
		21d, discontinue permanently PSB202 and continue follow-up per protocol. • Permanently discontinue PSB202 for any recurrence of Grade 3 toxicity
	Grade 4 • >10.0 × ULN if baseline was normal; • >10.0 × baseline if baseline was abnormal	• Close monitoring • Discontinue permanently PSB202 and continue follow-up per protocol.
Combined elevation of ALT/AST and TBL (Hy's Law)	ALT/AST > 3× ULN and concomitant TBL > 2× ULN in the absence of evidence of biliary obstruction (i.e., no significant elevation of ALP) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis)	• Close monitoring • Discontinue permanently PSB202 and continue follow-up per protocol.

Close monitoring includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Consider gastroenterology or hepatology consultations.

6.3 Prior and Concomitant Medications

6.3.1 General

Concomitant medications will include ongoing medications and all medications that were administered within 14 days prior to the planned start of study drug through the SFU visit (at least 21 days [+7 days] after the last dose of study drug) and are to be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins, nutritional supplements, and other remedies. Excluded medications are indicated in the Exclusion Criteria (Section 4.2).

6.3.2 Pre-Medication and Allowed Concomitant Medications

Standard pre-infusion medications (650-1000 mg acetaminophen and anti-histamine) will be provided 30-60 minutes prior to study drug infusion, and the glucocorticoid (10-20 mg dexamethasone or 40-80 mg methylprednisolone or equivalent other steroid) are recommended be provided prior to PSB202 infusions in Cycle 1. In later cycles, with IRR absent or less intense, aim to avoid steroids if feasible, as steroids may interfere with tumor response evaluation. Patients deemed at increased risk for tumor lysis syndrome (high tumor burden, absolute lymphocyte count $\geq 25 \times 10^9$/L will be provided with anti-hyperuricemics (e.g. allopurinol or rasburicase) pre-infusion. PEPCID may be added per investigator discretion.

Standard supportive medications may be used in accordance with institutional guidelines and Investigator discretion. These may include hematopoietic growth factors to treat neutropenia, anemia, or thrombocytopenia in accordance with American Society for Clinical Oncology guidelines; red blood cell (RBC) and platelet transfusions; anti-emetic, analgesic, and antidiarrheal medications; electrolyte repletion (e.g., calcium and magnesium) to correct low electrolyte levels; glucocorticoids (approximately 20 mg per day prednisone or equivalent for ~ 14 days, unless there is a compelling clinical rationale for a higher dose articulated by the Investigator and approved by the Sponsor), including short courses to treat asthma, chronic obstructive pulmonary disease, etc.; thyroid replacement therapy for hypothyroidism; and bisphosphonates, denosumab. and other medications for the treatment of osteoporosis, prevention of skeletal-related events from bone metastases, and/or hyperparathyroidism. Continuation of standard of care medications, including hormonal therapy for patients with prostate cancer (e.g., gonadotropin-releasing hormone [GnRH] or luteinizing hormone-releasing hormone [LHRH] agonists) and breast cancer (e.g., GnRH/LHRH agonists, aromatase inhibitors, selective estrogen receptor modulators [SERMs] or degraders [SERDs]), that the patient has been on for the previous 28 days, are allowed, provided they are not on the list of prohibited concomitant medications (refer to Section 6.3.3). Prophylactic antimicrobial agents may be used at the discretion of the Investigator. Local treatment while receiving

PSB202 (e.g., palliative radiation therapy or surgery for bone metastases) is permitted with documented Sponsor approval; however, the Sponsor recommends holding PSB202 for ~3-5 half-lives before and after radiation therapy or surgery. Any concern for disease flare due to a prolonged PSB202 dose interruption should be discussed with the Sponsor, who may permit holding PSB202 for a shorter period of time.

6.3.3 Prohibited Concomitant Medications

Except as indicated in Section 6.3.2, patients are not allowed to receive concomitant systemic anti-cancer agents, therapeutic monoclonal antibodies, drugs with immunosuppressant properties, or any other investigational agents besides PSB202. No new, alternative systemic anticancer therapy is allowed prior to documentation of PD in accordance with protocol-specified disease response criteria. Any exceptions to the above must be approved by the Sponsor.

6.3.4 Contraindications

PSB202 is contraindicated in patients with known hypersensitivity to any of its components.

6.4 Removal of Patients from Therapy or Assessment

Patients will be advised that they are free to discontinue study treatment at any time and that they will be followed for survival after discontinuing treatment (refer to Section 7.2). Over the course of the study, the Investigator and/or the Sponsor should remove a patient from treatment for any of the reasons listed below:

- PD by disease-defined criteria
- Unacceptable toxicity
- Pregnancy
- Requirement for alternative treatment in the opinion of the Investigator, unless such treatment is temporary (e.g., local radiation or surgery for disease that does not meet the definition of PD)
- problems with patients' compliance
- Withdrawal of consent by the patient
- Loss to follow-up
- Death
- Study terminated by Sponsor

At the time a patient discontinues treatment, all safety data normally required at the EOT visit will be obtained if possible, as outlined in Section 7.1.6. Patients will enter LTFU where they may be required to undergo disease assessments (refer to Section 7.1.8).

6.5 Reasons for End of Study

Reasons for end of study could be:

- Withdrawal of consent by the patient
- Loss to follow-up
- Death
- Study terminated by Sponsor

7 STUDY PROCEDURES AND ASSESSMENTS

Descriptions of assessments are provided in Sections 7.1 through 7.1.8, below. Specific timing requirements for study procedures and assessments are provided in **Table 6**.

Additional guidance for study assessments and procedures and collection of samples for central assessments (Phase 1b only) is provided in Appendix H and the Laboratory Manual.

Table 6 Schedule of Assessments

Evaluation	**Screening**	**Cycle 1**				**Cycles 2 through 9**	**Intra-patient Dose Escalation**	**EOT**	**SFU**	**LTFU**
Visit Window	**(Day -28 to Day 0)**	**Day 1 ± 2 Days**	**Day 2 ± 2 Days**	**Day 8 ± 2 Days**	**Day 15 ± 2 Days**	**± 3 Days**	**Day 1 ± 3 Days**	**+7 days of last dose or decision to terminate treatment**	**21 days (+ 14 days) after last dose**	**Every 3 months ± 14 Days**
Informed consent	X									—
Medical, surgical, malignancy history[1]	X	—	—	—	—	—	—	—	—	—
Pathology/molecular report(s) confirming histologic diagnosis and relevant biomarkers[2]	X	—	—	—	—	—	—	—	—	—
Confirmation of archived nodal/tumor tissue or fresh biopsy[3]	X	—	—	—	—	—	—	—	—	—
Bone marrow aspirate and biopsy[3,4]	X	—	—	—	—	—	—	—	—	—
Peripheral blood[5]	X	—	X	—	—	X	—	X	—	—
Serum or urine pregnancy test (if applicable)[6]	X	X	—	—	—	Day 1 each cycle	—	—	—	—
Physical examination and ECOG[7]	X	X	—	X	X	Day 1 each cycle	X	X	X	—
Vital signs[8]	X	X	X	X	X	Day 1 each cycle	X	X	X	—

Evaluation	**Screening**	**Cycle 1**				**Cycles 2 through 9**	**Intra-patient Dose Escalation**	**EOT**	**SFU**	**LTFU**
Visit Window	**(Day -28 to Day 0)**	**Day 1 ± 2 Days**	**Day 2 ± 2 Days**	**Day 8 ± 2 Days**	**Day 15 ± 2 Days**	**± 3 Days**	**Day 1 ± 3 Days**	**+7 days of last dose or decision to terminate treatment**	**21 days (+ 14 days) after last dose**	**Every 3 months ± 14 Days**
12-lead ECG[9]	X	X	—	X	—	Day 1 Cycles 2 through 9 then as clinically indicated	X	X	X	—
SPEP, serum immunofixation, serum FLC (optional), quantitative immunoglobulins[10]	X	X	—	—	—	±7 days of each radiologic disease assessment	—	X	—	—
B2 microglobin[11]	X	—	—	—	—	—	—	—	—	—
Serum viscosity, cold agglutinins, anti-myelin, ganglioside M1, sulfatide IgM, cryoglobulins, amyloid[12]	X	—	—	—	—	—	—	—	—	—
HIV, CMV, HEV, hepatitis B/C serologies, Covid-19 [13]	X	—		—	—	—	—	—	—	—
Hematology[14]	X	X	X	X	X	Day 1 each cycle	X	X	X	—
Serum chemistries[15]	X	X	—	X	X	Day 1 each cycle	X	X	X	—

Evaluation	**Screening**	**Cycle 1**				**Cycles 2 through 9**	**Intra-patient Dose Escalation**	**EOT**	**SFU**	**LTFU**
Visit Window	**(Day -28 to Day 0)**	**Day 1 ± 2 Days**	**Day 2 ± 2 Days**	**Day 8 ± 2 Days**	**Day 15 ± 2 Days**	**± 3 Days**	**Day 1 ± 3 Days**	**+7 days of last dose or decision to terminate treatment**	**21 days (+ 14 days) after last dose**	**Every 3 months ± 14 Days**
Coagulation panel[16]	X	As clinically indicated								
Urinalysis[17]	X	X	—	—	—	Day 1 every 2nd cycle	—	X	—	—
Blood sample(s) for PK[18]	—	X	—	X	X	Day 1 Cycles 3 and 6	X	—	—	—
Anti-drug antibodies[19]	X	—	—	—	X	Day 1 Cycles 2, 3 and 4 then D1 every other cycle	—	X	—	—
Blood for MRD[20]	X					Conduct after CR/CRi				
Disease assessment[21]	X	—	—	—	—	Every 8 weeks beginning with C3 (±7 days)	—	For non-PD, after 9 cycles, every 12 weeks (± 14 days)		
Survival status	—	—	—	—	—	—	—	—	—	X
PSB202 administration[22]	—	X	—	X	X	X	X	—	—	—
Concomitant medication[23]	→									

Evaluation	Screening	Cycle 1				Cycles 2 through 9	Intra-patient Dose Escalation	EOT	SFU	LTFU
Visit Window	**(Day -28 to Day 0)**	**Day 1 ± 2 Days**	**Day 2 ± 2 Days**	**Day 8 ± 2 Days**	**Day 15 ± 2 Days**	**± 3 Days**	**Day 1 ± 3 Days**	**+7 days of last dose or decision to terminate treatment**	**21 days (+ 14 days) after last dose**	**Every 3 months ± 14 Days**
Adverse events[24]	→								→	

Abbreviations (for Table 6 and Footnotes): AE-adverse event; ALT-alanine aminotransferase; AST-aspartate aminotransferase; aPTT-activated partial thromboplastin time; BUN-blood urea nitrogen; cfDNA-circulating free tumor deoxyribonucleic acid; CMV-cytomegalovirus; CR-complete response; CRi-complete response with incomplete hematologic response; D-day; DAT-direct antiglobulin test; DNA-deoxyribonucleic acid; ECG-electrocardiogram; ECOG-Eastern Cooperative Oncology Group; eCRF-electronic case report form; EOT-End of Treatment; *i.v.*-intravenous; HbA1c-hemoglobin A1c; HBsAg-hepatitis B surface antigen; HBsAb-hepatitis B surface antibody; HBcAb-hepatitis B core antibody; HCV-hepatitis C virus; HIV-human immunodeficiency virus; ICF-informed consent form; IgE-immunoglobulin E IgG- immunoglobulin G; IgM- immunoglobulin M; INR-international normalized ratio; LDH-lactate dehydrogenase; LTFU-long-term follow up; MRD-minimal residual disease; PCR-polymerase chain reaction; PK-pharmacokinetics; PR-partial response; PRi-partial response with incomplete hematologic response; PT-prothrombin time; PTT-partial thromboplastin time; RBC-red blood cell; SAE-serious adverse event; SFU-safety follow-up; WBC-white blood cell.

Footnotes for Table 6:

[1]All conditions ongoing and relevant past surgical and medical history should be collected. Cancer history should be collected regarding disease under study as well as any history of other malignancy on the appropriate eCRF.

[2]Refer to Appendix F for guidance regarding confirmation of histological diagnosis and relevant biomarkers per disease type. For all patients, anonymized/redacted report(s) to be submitted to Sponsor or designee during Screening /prior to enrollment. Additional information is provided in Section 7.6.

[3]Refer to Appendix F for guidance regarding requirements for sample submission based on histology. If a specific sample is unavailable, contact the Sponsor for additional guidance. Sample requirements for SLL and WM include: (1) bone marrow aspirate and biopsy obtained after most recent treatment; (2) fresh peripheral blood sample. Tissue requirements for MZL include: (1) archived nodal/tissue sample; (2) bone marrow aspirate and biopsy obtained after most recent treatment (splenic MZL subtype); (3) fresh peripheral blood sample. For other NHL, sample requirements include: (1) archived nodal/tissue sample; (2) bone

marrow aspirate and biopsy obtained after most recent treatment; (3) fresh peripheral blood sample. If bone marrow biopsy and aspiration was done within 90 days of screening and samples are available, these do not need to be repeated. For MZL and other NHL, if archived nodal/tissue sample is not available or inadequate, a fresh sample should be obtained if biopsy is safe to perform. Provision of select samples may be waved with documented Sponsor approval.

[4]Bone marrow aspirate and biopsy is required to confirm CR for WM, CLL patients and for other NHL patients (e.g., FL, transformed FL/CLL) if performed at baseline and known to be positive for disease involvement. Refer to Appendix F for guidance regarding sample requirements per histology. Additional information is provided in Section 7.7.

[5] Peripheral blood for PD and biomarker analysis (Phase 1a only)

Flow cytometry may be performed locally of local lab capacity is available. If not, Sponsor representative will arrange transport to a reference lab. See for further instructions the Laboratory Manual.

[6]All women who are not postmenopausal (and 2 years of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening within 7 days before Cycle 1 Day 1. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to Day 1 of each subsequent cycle of study treatment (laboratory samples may be obtained up to 72 hours before start of study treatment administration on Day 1 of the treatment cycle). Additional information is provided in Section 7.1.9.7.

[7]Physical examination including neurological exam and review of relevant systems at Screening, body weight, and height. Symptom-directed physical examinations, including measurement of weight may be performed at other time points. Additional information is provided in Section 7.1.5

[8] At each visit, to assess vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

[9]Triplicate ECGs should be performed during Screening and during Cycle 1 at the following time points: pre-dose (up to 4 hours pre-dose), Cycle 1 Day 1 at 2 and at 4 hours post-dose (±10 minutes), and Cycle 1 Day 8 at 2 and at 4 hours post-dose (±10 minutes). In addition, triplicate ECGs should be obtained at 2 hours post-dose (±10 minutes) on Day 1 of Cycles 2 through 6. Additional ECGs may be performed if clinically indicated. For intra-patient dose escalation, triplicate ECGs should be performed pre-dose (up to 4 hours pre-dose) on Day 1 of the patient's new dose, and at 2 and at 4 hours post-dose (triplicate, ±10 minutes) on Days 1 and 8 of the patient's new dose.

[10]For all WM patients and other patients if present at baseline or clinically indicated in the opinion of the Investigator.

[11]In addition to local assessment (Phase 1a), during Phase 1b, a blood sample for central assessment of beta-2 microglobulin at baseline should be collected for specific disease histologies. Collection guidelines are provided in Appendix F.

[12]Collect for WM patients if clinically indicated.

[13] Hepatitis B surface antigen (HBsAg) and antibody along with hepatitis B core antibody should be obtained. An additional sample should be obtained for evaluation of the hepatitis B DNA titer if the HBsAg is positive. Hepatitis C antibody should be obtained. An additional sample should be obtained for evaluation of hepatitis C RNA titer if the antibody test is positive. Additional information is provided in Section 7.1.9.7. For subjects from China sites only, treponema pallidum (TP) antibody testing should be performed, and if the antibody test is positive, additional samples should be obtained for RPR evaluation.

[14]Hematology includes hemoglobin, hematocrit, RBC count, WBC count, platelet count, percent or absolute WBC count differential (neutrophils, bands, lymphocytes, eosinophils, basophils, and monocytes) and lymphocyte subsets (T, B, NK cells). Flow cytometry is required during Phase 1a only, and only during protocol specified PD time points-see also Footnote 5 and the Laboratory Manual. In addition, in Phase 1b only, blood samples for central assessment of hematology parameters should be collected for specific disease histologies. Collection guidelines are provided in Appendix F.

[15]Serum chemistry includes sodium, potassium, chloride, bicarbonate, glucose, BUN/urea, creatinine, calcium, magnesium, phosphorus, total bilirubin, direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, LDH, uric acid/urate. In addition to local assessment, a blood sample for central assessment of LDH at baseline should be collected for specific disease histologies. Collection guidelines are provided in Appendix F.

[16]Coagulation panel includes aPTT and PT (INR).

[17]Urinalysis includes color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen.

[18] For the Phase 1a part of the study: Blood samples for PK should be collected pre-dose on C1D1, C1D8, C1D15 (only if PSB202 dosing is done on C1D15), with 2 samples on C1D1 and C1D8, 3 samples on C1D15 (within 30 minutes pre-dose and at 15 minutes post completion of dosing and for C1D15 a third sample 2 hours (+/- 15 minutes) post dosing prior to discharge). In the event that the Safety Review Committee drops the Cycle 1, Day 15 PSB202 infusion from the dosing schedule at higher dose levels, the Cycle 1 Day 16 visit is no longer needed, and PK-sampling associated with C1D15 is dropped. On C3D1 and C6D1, just one PK-sample is collected within 30 min pre-dose. For the Phase 1b part of the study, sparse PK will be performed. Select centers may opt into to a separate "Intense PK" sub-protocol with additional sampling (APPENDIX H). Provided infusion is done, on C1D1, C1D8, and C1D15 samples will be drawn pre-dose and immediately after end-of-infusion (EOI). A single PK-sample at C2D2 will be drawn only if C2D1 is the first day of the highest dose tested in the cohort. In the event the dosing schedule at higher Phase 1a dose levels shifts to "step-up dosing" and C2D1 becomes the first day of the highest dose level tested in the cohort, the blood count safety labs and PK-sampling from Table 6 shifts: C1D15 and C1D16 PK-sampling is dropped, and shifts, respectively, to C2D1 and C2D2. Refer to Section 7.2 for further guidance on PK-sampling.

[19] For patients in the 1a part of the study, obtain samples for the assessment of anti-drug antibodies at baseline (prior to dosing at Cycle 1), Day 15 of Cycle 1, and prior to dosing for Cycles 2, 3 and 4, then every 2 cycles beginning at Cycle 6, and at end of treatment. Neutralizing antibodies (Nab) will be assessed (once assessment is available) only in patients with treatment-emergent ADA. Additionally, ADA samples will be collected at the time of a ≥ Grade 3 infusion-related event, and 30 days after the event.

[20]Peripheral blood sample for MRD analysis in CLL patients at Cycle 1 Day 1 (prior to dosing), then 8 weeks (±1 week) after CR/CRi and then every 12 weeks (±4 weeks) until MRD negative, then assess MRD in bone marrow.

[21]Refer to Appendix C, Appendix D and Appendix E for specific disease assessment guidelines. Tumor evaluations are conducted at every 3 cycles (±7 days) since first dose, such as C3D1 ±7 days (week 7 ±7 days), C6D1 ±7 days (week 16 ±7 days), C9D1 ±7 days (week 25 ±7 days). After completing 9 cycles of treatment, tumor evaluation should be conducted every 12 weeks (±14 days) up to 2 years or the end of the study. A confirmatory tumor evaluation after the first tumor evaluation that shows a CR o by disease-specific criteria, if consistent with local regulatory authority requirements, combine bone marrow aspirate and/or biopsy with PET-CT scan should be used together with a contrast-enhanced CT scan, instead of CT scanning based on clinical practice.

[22]Includes PSB202 dosing, in Cycle 1 at D1, D8 and D15 (loading doses), then Q3 weeks (D1 of each 3-week cycle) until EOT. In the event of intra-patient dose-escalation in a Phase 1a patient, the new (higher) dose is administered in standard 3-week cycles only, i.e. no additional D8 and D15 loading doses are provided at the higher dose level.

[23]Concomitant, ongoing medication(s) plus those administered within 28 days prior to the planned start of treatment.

[24]AEs and SAEs should be recorded from the time that written informed consent has been obtained through the SFU Visit.

7.1 Study Assessments

7.1.1 Informed Consent

Patients must be able to provide written informed consent and meet eligibility criteria prior to enrollment. Separate ICFs will be required for patients enrolling in phase 1a and in phase 1b. Additional details are provided in Section 10.1.3.

7.1.2 Screening

The screening procedures must be conducted within 28 days of C1D1, unless otherwise noted. Patients who cannot complete the procedures within the screening window may be rescreened, and certain screening procedures may not need to be repeated, including certain procedures that were obtained as part of the patient's standard care prior to providing informed consent for this study, with documented Sponsor approval. Screening tests that are completed in the 48 hours prior to start of study drug administration and that duplicate C1D1 tests according to the Schedule of Assessments **Table 6**) will be accepted as fulfilling the C1D1 assessments; repeat testing on C1D1 is not necessary for this scenario, and results should be recorded in the Screening set of eCRFs.

7.1.3 Enrollment

Enrollment procedures will be conducted in accordance with the Schedule of Assessments (**Table 6**). Patients who meet eligibility criteria outlined in Section 4 will be enrolled in this study. A patient may be enrolled into either phase 1a or phase 1b of the study, but not both. In both phase 1a and 1b, the Investigator may repeat qualifying laboratory tests and vital signs/ ECGs prior to enrollment if a non-qualifying finding is considered an error, and/or if an acute finding is likely to meet eligibility criteria on repeat testing.

7.1.4 Medical and Surgical History, and Demographics

All conditions ongoing and relevant past surgical and medical history should be collected. Medical, surgical, and malignancy history, including the disease under study as well as history of any other malignancy, diagnosis dates, prior treatments for the malignancy, etc. should be recorded on the appropriate eCRF. Demographics including age, gender, race, and ethnicity will be recorded.

7.1.5 Physical Examination

Physical examinations will be conducted in accordance with the Schedule of Assessments (**Table 6**) and will include neurological exam and review of relevant systems at Screening, body weight, and height. Symptom-directed physical examination may be performed at other time points after Screening in accordance with the Schedule of Assessments (**Table 6**). T 和 specific physical examination of lymphoma needs to be recorded in the eCRF, including superficial lymph nodes, liver, spleen, tonsils, and other lymphoma features involving the body surface.

7.1.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status will be assessed in all patients in accordance with the Schedule of Assessments (**Table 6**). The ECOG performance scale is provided in Appendix G. The ECOG performance status will assist in assessing how a patient's disease is progressing, assessing how the disease affects the daily living abilities of the patient, and determining the appropriate treatment and prognosis.

7.1.7 Vital Signs

Vital signs will be measured pre-dose in accordance with the Schedule of Assessments (**Table 6**) and should include systolic and diastolic blood pressure, heart rate, respiratory rate, weight and body temperature.

At PK time points, vital signs should be assessed as indicated in the Schedule of Assessments (**Table 6**), prior to actual PK blood sampling at these time points.

7.1.8 Electrocardiograms

Twelve-lead resting ECGs will be performed in accordance with the Schedule of Assessments (**Table 6**). To minimize variability, it is important that patients are in a resting position for at least 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG to prevent changes in heart rate. ECGs for each patient should be obtained from the same machine whenever possible. When ECGs coincide with PK draw days, ECGs should be performed before the PK blood draw. Any clinically significant changes in ECGs that occur during the study should be reported as an AE in the eCRF.

7.1.9 Laboratory Tests

Local laboratories will be utilized for routine laboratory tests, for example, serum chemistries, hematology, and urinalysis. In Phase 1a, PK samples will be assessed centrally. Starting in Phase 1b (cohort expansion), certain laboratory test samples will be collected for later central response evaluation (e.g., complete blood count and lymphocyte subsets for CLL patients, SPEP/immunofixation/sFLC/quantitative Igs for WM patients). PK studies will always be performed centrally. Additional guidance regarding testing and handling and processing of samples for central assessment is provided in Appendix H and the Laboratory Manual.

7.1.9.1 Hematology

Hematology should be assessed in accordance with the Schedule of Assessments (**Table 6**) and should include assessment of the following: WBC count, hemoglobin, hematocrit, RBC count, percent or absolute WBC count differential (neutrophils, lymphocytes, eosinophils, basophils, and monocytes), and platelet count. In Phase 1b, blood samples for central assessment should also be collected for CLL patients on C1D1, ±7 days of each radiologic disease assessment and at disease progression.

7.1.9.2 Serum Chemistries

Serum chemistries should be assessed in accordance with the Schedule of Assessments (**Table 6**) and should include assessment of the following: Sodium, potassium, chloride, bicarbonate, glucose, BUN/urea, creatinine, calcium, magnesium, phosphorus, total protein, albumin, total bilirubin, direct bilirubin, ALT, AST, alkaline phosphatase, uric acid/urate, and LDH.

7.1.9.3 β2 microglobulin

In FL patients only, β2 microglobulin should be collected on C1D1 prior to dosing. It is recognized that results of this test will not be available until after dosing. In responding FL patients (PR or CR only), β2 microglobulin status will be repeated at the time or response confirmation.

7.1.9.4 Coagulation

The coagulation panel should include aPTT and PT (INR) and should be assessed during Screening and then only as clinically indicated.

7.1.9.5 Urinalysis

Urinalysis should be assessed in accordance with the Schedule of Assessments (**Table 6**) and should include color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, protein, leukocytes, nitrites, and urobilinogen.

7.1.9.6 Pregnancy Testing

Pregnancy testing (serum or urine) should be conducted in accordance with the Schedule of Assessments (**Table 6**). Pregnancy reporting information is provided in Section 9.6. All women who are not postmenopausal (and 2 years of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. In addition, for women of childbearing potential, a serum or urine pregnancy test must be performed prior to Day 1 of each subsequent cycle of study treatment. If any urine pregnancy test is positive, study treatment will be delayed until the patient pregnancy status is confirmed by a serum pregnancy test. If serum pregnancy test is positive, the patient will be permanently discontinued from study treatment.

7.1.9.7 Viral serologies: HIV, CMV, Hepatitis B/C

Viral serologies should be assessed at baseline in accordance with the Schedule of Assessments (**Table 6**) and should include testing for HIV (if HIV status is not known), CMV (e.g. quantitative PCR, antigenemia), hepatitis B (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], and total hepatitis B core antibody [HBcAb]) and hepatitis C virus (HCV) antibody serology. Patients with a positive HIV test are excluded from participation in the trial due to potential drug-drug interactions between anti-retroviral medications and PSB202 and risk of opportunistic infections. Patients with a known medical

history of Covid-19 infection should confirm Covid-19 negative status by PCR at the time of screening.

7.1.9.8 Lymphocyte subsets

Lymphocyte subsets should be assessed in CLL patients in accordance with the Schedule of Assessments (**Table 6**) and should include T-cell, B-cell and NK cell subsets and absolute B-cell count. In Phase 1b, blood samples for later central assessment should also be collected in accordance with the Schedule of Assessments (**Table 6**).

7.1.9.9 SPEP, Serum Immunofixation, Serum FLC, Quantitative Immunoglobulins

SPEP, serum immunofixation, serum FLC, and quantitative immunoglobulins should be assessed in WM patients (and other patients if M-protein known to be present at baseline) in accordance with the Schedule of Assessments (**Table 6**). In Phase 1b only, blood samples for later central assessment should also be collected in accordance with the Schedule of Assessments (**Table 6**).

7.2 Pharmacokinetics

For phase 1a patients, PK samples should be collected in accordance with the Schedule of Assessments (**Table 6**). Additional PK assessments may be conducted in patients when considered necessary by the Investigator to understand exposure in relationship to possible safety or efficacy findings or if there is a change to the formulation of PSB202 administered.

For patients for whom additional PK-sampling is feasible, i.e. because they are hospitalized, an "intense PK" sampling schedule with more frequent sampling than directed in Table 6 is specified in APPENDIX H, **Table 1a, 1b and 1c**. The "Intense PK" sampling schedule is designed to be adaptive to the dosing schedule established prior to initiating each cohort, such as to focus the PK-sampling in the week that follows the first administration of full-dose PSB202 in the cohort:

(a) In a cohort of priming dose or step-up dosing where C1D8 or C1D15 is the first day of full-dose PSB202 administration, additional PK-samples are collected 24 hours, 48hours, 72 hours and 120 hours post dosing. See Table 1a and 1b.

(b) In a cohort of step-up dosing where C2D1 is the first day of full-dose PSB202 administration, additional PK-samples are collected on C2D2, C2D3, C2D6, C2D8 and C2D15. See Table 1c.

Clinics with the ability to conduct such more "intense PK" sampling per APPENDIX H may opt into this with consenting patients, whereas clinics who cannot conduct "intense PK" will conduct PK-sampling according to Table 6, footnote 18.

In the event that study drug is NOT dosed, no PK-sampling associated with that dose is done.

If a patient undergoes intra-patient dose escalation, 3 plasma samples (same time points as during C1D1) for PK analysis should be obtained on Day 1 of a patient's new dose. Such additional PK collection is required only after the first dose escalation, not following any second- or subsequent escalations.

In Phase 1a patients, the plasma concentration of PSB202 will be determined with a validated bioanalytical assay and used to calculate PK parameters as described in Section 8.4.4. These parameters will be used to assess linearity of exposure and accumulation of drug exposure with time. Exploratory analyses to determine the presence and structures of metabolites of PSB202 may also be conducted and the results of these analyses, if conducted, will be reported separately by the Sponsor. Concentrations of PSB202 may also be used for population-PK analyses, to be reported separately by the Sponsor.

For the Phase 1b part of the study sparse PK will be performed per Table 6 (Schedule of Assessments). On C1D1, C1D8, and C1D15 samples will be drawn pre-dose and immediately after end-of-infusion (EOI). For patients participating in "Intense PK", On C2D1, the intensive PK-sampling schedule should be collected according to Table 6d. A single sample will be drawn pre-dose on C4D1, C6D1 and C8D1.

7.3 Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (NAb)

For patients in the 1a part of the study, obtain samples for the assessment of anti-drug antibodies at baseline (prior to dosing at Cycle 1), Day 15 of Cycle 1, and prior to dosing for Cycles 2, 3 and 4, every 2 cycles beginning at Cycle 6, and at the end of treatment visit. Presence of neutralizing antibodies will be assessed (once assessment is available) only in patients with treatment-emergent anti-drug antibodies. ADA samples will also be collected at the time of any ≥ grade 3 infusion-related events and 30 days after the event.

7.4 Telephone Follow-up

The site will contact the patient by telephone in accordance with the Schedule of Assessments (**Table 6**) to assess for PSB202 tolerability, continuation of study drug, and whether the patient needs to return to clinic earlier than planned. If not tolerating the drug well, the patient should be seen at least every 14 days to assess AEs, and the patient should be contacted regularly to assess AE status.

7.5 Confirmation of tumor sample obtained after most recent treatment (Phase 1b)

For Phase 1b patients only, confirmation of the availability of a tumor sample obtained after the most recent treatment should be provided during Screening. Any source of tumor sample (e.g. peripheral blood, bone marrow, nodal/extranodal tissue site) is acceptable, as long as the sample is of sufficient quantity and quality to allow molecular analysis. Refer to the Laboratory Manual for tumor sample requirements. If tumor sample after the most recent treatment is not available, a fresh sample should be obtained if safe to do so in the opinion of

the Investigator. If a fresh sample cannot be obtained safely, the patient may still be eligible with documented Sponsor approval.

7.6 Pathology and Molecular Reports

Anonymized/redacted pathology report(s) confirming histologic diagnosis and relevant biomarkers (e.g. FISH, IGVH, p53 and karyotype for CLL; MYD88 and CXCR4 status for WM; Ki67 staining for MCL) should be submitted. Status determined after most recent treatment is preferred and should be determined in a laboratory with certification by CLIA, ISO/IEC, CAP or equivalent.

7.7 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy should be collected during Screening. Bone marrow aspirate and biopsy is required to confirm CR for patients with WM, CLL and for other NHL patients (e.g., FL, MZL and MCL) if performed at baseline and known to be positive for disease involvement. Samples for central assessment should also be collected in accordance with the Schedule of Assessments (**Table 6**). If a bone marrow biopsy and aspiration was done after the last treatment and within 90 days of Screening and samples are available, these do not need to be repeated during Screening. Guidance on sample collection and timing is provided in Appendix H and the Laboratory Manual

7.8 Radiologic Disease Assessment

Radiologic disease assessment will be conducted by the Investigator in accordance with the Schedule of Assessments (**Table 6**) and the Imaging Manual. Investigators should use the same method consistently for an individual patient throughout the study. Assessments of both measurable and non-measurable disease will be made by the Investigator using criteria as appropriate to cancer type. All the measurable and evaluable lesions should be assessed and documented at screening, and re-assessed at each subsequent tumor evaluation, using hematological test, physical examination and CT scan (neck, thorax, abdomen and pelvis) for contrast-enhanced CT scan. Magnetic resonance imaging (MRI) or a PET-CT scan (only FDG-avid subtypes such as FL and MCL) may be used instead of CT scan for the patients with contraindications to CT scan. The following Appendices should be referred to for specific radiologic disease assessment information:

- Appendix C Chronic Lymphocytic Leukemia Response Assessment (iwCLL)
- Appendix D Waldenström Macroglobulinemia Response Assessment (iwWM)
- Appendix E Lugano Classification of Response in Non-Hodgkin's Lymphoma (MCL, FL, MZL and other NHL)

Tumor evaluations are conducted at every 3 cycles (±7 days) since first dose, such as C3D1 ±7 days (week 7 ±7 days), C6D1 ±7 days (week 16 ±7 days), C9D1 ±7 days (week 25 ±7 days). After completing 9 cycles of treatment, tumor evaluation should be conducted every 12 weeks (±14 days) up to 2 years or the end of the study. A confirmatory tumor evaluation

after the first tumor evaluation that shows a CR o by disease-specific criteria, if consistent with local regulatory authority requirements, combine bone marrow aspirate and/or biopsy with PET-CT scan should be used together with a contrast-enhanced CT scan, instead of CT scanning based on clinical practice.

In Phase 1b, patients who discontinue from the study for reasons other than disease progression prior to the Week 16 tumor evaluation may be replaced to ensure that an adequate number of response-evaluable patients is available for analysis.

7.9 Survival Status

For two years following enrollment, patients will be followed for survival status, date of progression, and subsequent anticancer therapy(ies) by telephone or other method.

7.10 Study Drug and Dosing Diary

Study drug should be administered in accordance with the Schedule of Assessments (**Table 6**) and Section 6. Completion of the dosing diary will include recording and time of PSB202 dosing, pre-medications (acetaminophen, anti-histamines, steroids if indicated) and any antacids, if given.

7.11 Concomitant Medication

Concomitant medications should be recorded in accordance with the Schedule of Assessments (**Table 6**).

All medications that were used from 28 days prior to enrollment through the end of study participation will be recorded in the eCRF. These are to include prescription and nonprescription medications, transfusions, vitamins and nutritional supplements, and other remedies. Excluded prior medications are excluded via the eligibility criteria (Section 4.2). Additional guidance regarding concomitant medications is provided in Section 6.3.

7.12 Adverse Events/Serious Adverse Events

Adverse events should be recorded in accordance with the Schedule of Assessments (**Table 6**) and Section 9.

7.13 Central Collection of Radiographic Studies and Samples (Phase 1b only)

During Phase 1a, disease status and disease progression are assessed by the investigator, guided by disease specific progression criteria appended to this protocol. Starting only in Phase 1b, post-hoc central evaluation of disease progression may complement the Investigator's assessment. During Phase 1b, baseline screening radiographic studies and all subsequent radiographic studies and their associated reports will be collected and stored to allow for future independent radiological review.

Similarly, in Phase 1b only, baseline and subsequent samples (peripheral blood, bone marrow aspiration and biopsy) required for response assessment according to disease-defined criteria will be collected and stored to allow for future independent review.

7.14 Samples at Progression after Treatment with PSB202

A fresh bone marrow aspirate and biopsy and/or tumor tissue biopsy (of node or extramedullary disease site) may be obtained at progression (both overt progression according to disease-defined criteria and if progression is not overt, but is suspected by the Investigator), if the patient provides informed consent, and if the tissue can be safely obtained (refer to **Table 7**). The purpose of obtaining these samples is to evaluate tumor changes that may have resulted from treatment. This sampling should only be collected if the patient has consented to collection and testing.

Because it is minimally invasive, peripheral blood collection at progression is required for CLL patients.

For biopsy procedures performed in the setting of PD, the Sponsor should be contacted and informed of the planned procedure, and whether or not therapy will be continued beyond progression or discontinued (EOT).

Table 7 Tissue/Whole Blood Sampling upon Progression

For patients who progress during therapy, biopsy upon progression should be done if clinically safe to perform and if patient consents. The clinician should consider if study therapy will continue beyond progression or be discontinued due to progression.	
Scenario	**Sampling**
At time of progression **where study therapy will be discontinued**	• Nodal/extranodal tumor tissue biopsy and/or bone marrow aspirate and biopsy from patients who experienced PD and consent to biopsy, if it does not jeopardize the patient's health • Whole blood for PBMCs and CD19+ cell isolation
At any progression, including if patient will continue study therapy as treatment beyond progression	• Nodal/extranodal tumor tissue biopsy and/or bone marrow aspirate and biopsy from patients who experienced PD and consent to biopsy, if it does not jeopardize the patient's health • Whole blood for PBMCs and CD19+ cell isolation

Abbreviations: cfDNA-circulating free tumor DNA; PD-progressive disease; PMBCs-peripheral blood mononuclear cells

7.15 Intra-Patient Dose Escalation

In Phase 1a, intra-patient dose escalation may be permitted following completion of the 28-day DLT period. Intra-patient dose escalation to next higher level may occur after all patients in the next (higher) dose cohort have completed the DLT observation period and the toxicity seen at the next (higher) dose has not exceeded the maximum tolerated dose (e.g., 0/3 or 1/6 patients experienced DLT). To be eligible for intra-patient dose escalation, the patient must have experienced no ≥ Grade 2 toxicity that is at least possibly related to study drug. Intra-patient dose escalation can be up to a level that is considered safe and beneficial to the patient by the Sponsor and Investigator based on the emerging safety and PK data from this

study. If a patient is dose escalated, procedures on Day 1 (±3 days) of the new dose should be performed as follows:

- Symptom-directed physical examination, weight, and ECOG score.
- Vital signs assessed at pre-dose (up to 4 hours pre-dose, as close to dosing as possible is preferred) and 2-hours post-dose (±15 minutes).
- Resting 12-lead ECGs conducted pre-dose (triplicate, up to 4 hours pre-dose), 2 hours post-dose (in triplicate, ±15 minutes) and 4 hours post-dose (triplicate, ±15 minutes).
- Hematology.
- PK (3 samples as on C1D1)
- Serum chemistries.

If Day 1 of the new dose falls on the same day (±3 days) of a previous hematology and serum chemistry assessment, it is not necessary to perform a repeat assessment (physical examination, vital signs, and ECGs must still be performed as indicated).

Requests for intra-patient dose escalation require Sponsor approval prior to treating a patient with a new dose. Treatment with a new dose should start on Day 1 (±3 days) of a cycle unless agreed otherwise with the Sponsor. After changed new dose, Investigors should closely follow up patients and monitor their safety.

Dose escalation is not allowed in Phase 1b.

7.16 End of Treatment

Within 7 days of last dose of study drug or at the time of premature discontinuation of treatment, the EOT assessments and procedures will be conducted in accordance with the Schedule of Assessments (**Table 6**). These should include scheduling of nodal/extranodal tumor tissue and/or bone marrow aspirate and biopsy from patients who experience PD if the patient provides informed consent, and if the tissue can be safely obtained.

7.17 Safety Follow-up

The safety follow-up (SFU) assessments will be conducted within 3 weeks (+14 days) of last dose of study drug in accordance with the Schedule of Assessments (**Table 6**) . SFU procedures may be performed as part of the EOT visit if the latter was performed at 21 days (±7 days) from EOT. .

7.18 Long-Term Follow-up

The LTFU assessments and procedures will be conducted in accordance with the Schedule of Assessments (**Table 6**). After treatment discontinuation, LTFU will occur approximately

every 3 months (± 14 days) for up to 2 years, until the patient experiences PD, withdraws consent for further participation, is lost to follow-up, has died, or close of the study. Assessments may include: subsequent anticancer therapy(ies) and survival status. Long-term follow up may be conducted by phone. For any patient who is lost to follow-up, the study site will attempt to ascertain survival information via public database search. If survival status still cannot be ascertained, patients will be considered lost to follow-up and will be censored appropriately.

If a patient discontinues study treatment for reasons other than PD, withdrawal of consent or initiation of a new anticancer therapy(ies), the patient is required to undergo disease assessment by imaging as specified in Appendix C, Appendix D, and Appendix E until PD (even if PD occurs after 2 years), withdrawal of consent, or initiation of a new anticancer therapy(ies), utilizing the same modality(ies) used for the baseline imaging assessment.

8 PLANNED ANALYSES

A full Statistical Analysis Plan (SAP) will provide specific details on the analytical methods and data displays.

8.1 Study Endpoints

Primary Endpoint (Phase 1a)

- DLT, guiding establishment of a MTD/RP1b Dose/recommended dose for further study.

Secondary Endpoints (Phase 1a)

- AEs and SAEs, changes in hematology and blood chemistry values, ADA, assessments of physical examinations, vital signs, and ECGs
- Plasma concentration of PSB202 and PK parameters including, but not limited to AUC_{0-t}, C_{max}, T_{max}, $T_{1/2}$, and degree of accumulation.
- ORR by Investigator.

Primary Endpoint (Phase 1b; for each cohort)

- ORR by Investigator

Secondary Endpoints (Phase 1b; for each cohort)

- ORR (by Central Review), BOR, DOR, PFS (by Investigator and IRC)
- AEs and SAEs, changes in hematology and blood chemistry values, ADA, assessments of physical examinations, vital signs, and ECGs
- Plasma concentration of PSB202 and PK parameters including, but not limited to AUC_{0-t}, C_{max}, T_{max}, $T_{1/2}$, and degree of accumulation.

Exploratory Endpoints

- Differences in efficacy and safety based on PSB202 PK parameters.
- MRD for those CLL/SLL patients with a clinical CR
- In FL patients only: peripheral blood bcl-2 re-arrangement (reversion to negative).

8.2 Analysis Populations

8.2.1 Safety Population

The safety population will be used primarily for the analysis of safety data and will consist of all enrolled patients who receive 1 or more doses of PSB202, including patients considered to have inadequate drug exposure and therefore are replaced for the determination of the MTD.

8.2.2 Full Analysis Set (FAS)

The FAS will be used primarily for the analysis of tumor response and other efficacy-related data. The FAS will include all patients enrolled in phase 1a (only those treated at the dose level ultimately chosen as the RP1B dose) and phase 1b who meet the following criteria:

- Measurable disease at baseline as assessed using iwCLL, iwWM or Lugano criteria, as appropriate to tumor type
- Receive at least 1 dose of study drug

The analysis populations for other trial objectives (e.g., PK, tumor markers) will be defined in the SAP.

8.3 Determination of Sample Size

Phase 1a – Dose Escalation

One to 6 patients will be enrolled in each dose cohort based on an Accelerated Titration design. Each patient will participate in only a single dose cohort for the purpose of DLT evaluation (though, as discussed in Section 3.3, after completion of the DLT evaluation period, intra-patient dose escalation may be permitted, provided that the patient is tolerating their current dose, and the dose level to which the patient will be escalated has already been evaluated, has a DLT rate of <33% and has been declared safe by the SRC).

One subject will be initially enrolled in Cohorts 1-3. If any subject in a single-patient cohort exhibits a Grade 2 or worse AE during Cycle 1 that cannot reasonably be attributed to underlying disease, other medical conditions, or concomitant medications, the Cohort will be expanded to 3 patients and from that point forward the study will follow a 3+3 design. Starting with Cohort 4 (300 mg), the study will become a traditional 3 + 3 design with 3 or 6 subjects treated at this- and subsequent dose levels depending on the incidence of DLTs. If no DLTs occur in a cohort of 3 subjects, a new cohort of 3 subjects will be treated at the next higher dose level. If 1 of 3 subjects in a cohort experiences a DLT, that cohort will be expanded to 6 subjects. If only 1 of the 6 subjects has a DLT, then the next cohort of 3 subjects will be treated at the next higher dose level. If 2 or more DLTs occur within a cohort, then that dose level will be above the MTD (the highest dose where no more than 1 of 6 subjects has experienced a DLT), and new subjects will be enrolled at the previous lower (tolerated) dose level until that cohort has 6 subjects. The MTD is the highest dose studied where ≤ 1 in 6 subjects experiences a DLT.

During the dose escalation phase, approximately 25-32 patients are estimated to be needed to define the MTD/RP1bD of PSB202. Dose cohorts previously declared safe by the SRC may be expanded with an additional ~ 5 patients to further investigate the tolerability, PK, and biological activity of PSB202. At the presumed RP1b Dose, the cohort will remain open until at least 6 patients with CLL/SLL and another 6 patients with iNHL/WM are evaluable for DLT to allow for a RP1bD to be determined independently for CLL/SLL versus iNHL/WM.

The total number of patients to be enrolled in the dose escalation phase is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD.

Phase 1b – Dose Expansion

Patients with R/R B-cell malignancies have overall response rates to 2nd generation CD20+ directed therapy and irreversible BTK inhibitors of 42.6%-90.5% in CLL (Byrd, Brown et al. 2014, Byrd, Harrington et al. 2016), 68% in MCL (Wang, Rule et al. 2013), 90.5% in WM (Treon, Tripsas et al. 2015) and 48% in MZL (Noy, de Vos et al. 2017). In addition, patients with relapsed-refractory disease after CD20+ directed antibody therapy and/or prior irreversible BTK inhibitors will have been more extensively pre-treated and may as a result have more treatment-refractory disease and worse performance status then newly diagnosed patients. Therefore, a clinically relevant response rate in patients with prior CD20+ directed antibody therapy and/or BTK inhibitor treatment is ~30% or more. For the 1b Expansion Cohorts, the treatment effect will be considered clinically meaningful if there are at least 4 responders out of 20 patients in a cohort. This event will occur with probability 0.893 (true positive rate) if the true ORR is 30%, and 0.133 (false positive rate) if the true ORR is 10%. The treatment will be considered ineffective if the true ORR is 10% or less.

Table 8 provides guidance for interpretation of the treatment effect for each cohort based on the observed ORR.

Table 8 Event Probabilities for a Range of True Response Rates

N=20 per Cohort	True Response Rate							
Number of Responders	**0.05**	**0.1**	**0.15**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**
≥1	0.642	0.878	0.961	0.988	0.999	1.000	1.000	1.000
≥2	0.264	0.608	0.824	0.931	0.992	0.999	1.000	1.000
≥3	0.075	0.323	0.595	0.794	0.965	0.996	1.000	1.000
≥4	0.016	0.133	0.352	0.589	0.893	0.984	0.999	1.000
≥5	0.003	0.043	0.170	0.370	0.762	0.949	0.994	1.000
≥6	<0.001	0.011	0.067	0.196	0.584	0.874	0.979	0.998

Abbreviations: N-number of patients; No.-number.

8.4 Statistical Methods

8.4.1 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics for all enrolled patients will be tabulated. Patients will be tabulated by dose cohort and overall.

8.4.2 Safety Analyses

Safety will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory values, vital signs, ECG results, and concomitant medications. Unless specified otherwise, the safety analyses will be conducted for the safety population defined in Section 8.2. The results of these analyses will be presented by study phase. Tabulations will be provided by dose cohort and overall.

Summary tables and listings will be provided for all reported TEAEs, defined as AEs that start on or after the first administration of study drug. The reported AE term will be assigned a standardized preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be summarized based on the number and percentage of patients experiencing the event by MedDRA System Organ Class and preferred term. The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator based on the conventions described in Section 9.3. In the event a patient experiences repeat episodes of the same AE, then the event with the highest severity grade and strongest causal relationship to study drug will be used for purposes of incidence tabulations.

Tabular summaries will be provided for:

- All TEAEs.
- TEAEs by relationship (yes, no) to study drug, underlying disease, other medical conditions, or concomitant medications, and maximum severity grade.
- TEAEs with action of study drug delayed/interrupted or treatment reduced.
- TEAEs with action of study drug discontinued.
- All SAEs.
- SAEs by relationship (yes, no) to underlying disease, other medical conditions or concomitant medications.
- SAEs with action of study drug delayed/interrupted or treatment reduced.

The observed DLT rate in each dose cohort will be calculated by the crude proportion of patients who experience DLT. Multiple concurrent AEs leading to DLT will be considered a

single DLT. The estimate of the DLT rate will be accompanied by a 2-sided 95% exact binomial confidence interval (CI).

All deaths that occur within 21 days of treatment discontinuation will be reported in a patient listing, which will include the primary cause of death and the number of days between the date of the last dose of study drug and death. For patients undergoing long-term follow-up, the duration of survival following the initiation of study drug will be summarized in a descriptive manner using the Kaplan-Meier method. A summary of the anticancer therapies received after discontinuation of study drug will be provided.

Hematology and serum chemistries will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range as follows:

- Baseline value
- Minimum post-baseline value
- Maximum post-baseline value
- Average post-baseline value
- Last post-baseline value.

Laboratory values will be assigned toxicity grades when available using the NCI CTCAE, version 5. For CLL patients, hematologic toxicity will be assessed by the grading scale for hematologic toxicity in CLL studies in the IWCLL guidelines. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of patients and their maximum grade shift. For analytes without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation.

All patients will have pre-treatment baseline vital signs and pre-dose measurements on Day 1 of each cycle. The results for each vital sign will be summarized in a descriptive manner by calculating the mean, standard deviation, median, and range by time point in the same manner described for laboratory values. For these analyses, the minimum, maximum, average, and last post-baseline value will be determined relative to the baseline vital sign measurements only. In addition, serial vital signs measurements will be obtained pre- and post-dose on the first day of each patient's PSB202 treatment in conjunction with serial PK sampling. For each patient, the vital signs change from the pre-dose value will be summarized in a descriptive manner. The Wilcoxon signed rank test may be used to assist in the identification of any systematic changes.

8.4.3 Efficacy Analyses

The primary analysis of efficacy will be based on the FAS which will include all patients who receive at least 1 dose of study drug and have measurable disease at baseline by disease-defined criteria. These analyses will be summarized by the specific B-cell malignancy (e.g., CLL, WM, MCL, MZL and the status of specific tumor gene mutations (e.g., *PLCG2* gene mutations in FL patients). Patients who meet phase 1b eligibility, but who enroll in the phase 1a portion at the dose level later chosen as the RP1bDose may be included in the phase 1b efficacy analyses, provided that source documentation and imaging used for response evaluation can be made available and stored for possible later central review.

ORR will be assessed using IWCLL (Appendix C), IWWM (Appendix D) or Lugano criteria (Appendix E), as appropriate to tumor type. The estimate of the ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of patients with best overall response of PR or better, based on IWCLL, IWWM or Lugano criteria as determined by IRC and by the treating Investigator. The estimates of the ORR will be accompanied by a 2-sided 95% CI. Waterfall plots will be used to depict graphically the maximum decrease from baseline in the sum of longest diameters of target lesions. The duration of overall response, PFS, and OS will be summarized descriptively for each cohort using the Kaplan-Meier method.

Waterfall plots will be used to depict graphically the maximum decrease from baseline in the SPD of target lesions.

DOR will be calculated for patients who achieve a response of PR or better. For such patients, DOR is defined as the number of months from the start date of the first documented response to the earlier of the documentation of definitive disease progression or death from any cause.

PFS will be derived for each patient as the number of months from the date of the first dose of study drug to the earlier of documented PD or death due to any cause. Patients who are alive and without documented PD as of a data analysis cutoff date will be right-censored according to the censoring methods described later in this section. Whenever appropriate, the same censoring methods will be used for DOR.

OS will be derived for each patient as the number of months from the date of the first dose of study drug to the date of death, irrespective of cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the last date the patient was known to be alive or data analysis cutoff date, whichever occurs first.

DOR and PFS will be summarized descriptively using the Kaplan-Meier method with 95% CIs calculated using Greenwood's formula. Median follow-up for each endpoint will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper and

Smith 1996). Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% CI.

For patients who meet one or more of the following conditions, DOR and PFS will be right-censored as appropriate:

- Patients with no baseline or post-baseline disease assessments unless death occurred prior to the first planned post-baseline assessment (in which case the death will be considered a PFS event)
- Patients who initiate subsequent anticancer therapy in the absence of documented PD
- Patients who die or have PD after missing 2 or more consecutively scheduled disease assessment visits
- Patients who are last known to be alive and without documented PD on or before the data cut-off date

For such patients, the progression or censoring date will be determined based on described conventions (U.S.-Food-and-Drug-Administration 2018).

Analyses of secondary and exploratory endpoints will be provided in the SAP.

8.4.4 Pharmacokinetic Analyses

Plasma concentrations of PSB202 will be determined with a validated bioanalytical assay. The following PK parameters will be calculated from plasma concentrations determined on C1D1, C1D8, C1D15 and Day 1 of Cycles 3 and Cycle 6, if appropriate: Cmax, Tmax, AUC0–t (area under the concentration vs time curve from time 0 to t), AUC0–∞, apparent oral clearance (CL/F), apparent volume of distribution (Vz/F), and T1/2. See also Section 7.2.

Summary statistics will be generated by dose cohort and across cohorts as appropriate.

8.4.5 Pharmacodynamic analysis

In Phase 1a, Pharmacodynamic analysis will be conducted by means of measuring CD19+ B-cell depletion by flow cytometry, pre-dosing and at follow-up time points coincident with ADA sampling, as indicated in the study schedule (**Table 6**). Flow cytometry may performed by the participating study center's local lab if it has the capability/capacity, but may also be referred to a central or regional lab if the local lab does not have such capacity. CD20+ evaluation may be performed on the first pre-dose specimen to confirm that the tumor is still CD20+ following prior treatments.

Serial Total Lymphocyte Counts will be summarized in support of the PD analysis.

9 ADVERSE EVENTS

An AE is any unfavorable medical occurrence in a patient administered an investigational product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product. All AEs, complaints, or symptoms that occur from the time informed consent is signed until the SFU are to be recorded on the appropriate eCRF (events that occur prior to consent are considered medical history). Documentation must be supported by an entry in the patient's source medical records. Laboratory test abnormalities considered by the Investigator to be clinically relevant should be reported in the eCRF as an AE. Each AE is to be evaluated for duration, severity, and causal relationship with the investigational product or other factors. Disease progression of the primary tumor in and of itself is captured as an efficacy assessment and should not be captured as an AE (including fatal AEs) unless the disease progression is assessed as related to study treatment. If toxicities due to PD exist and are new or worsened from baseline, these should be reported as AEs. If a new primary malignancy appears, it will also be considered an AE.

9.1 Safety Review Committee

An SRC, comprised of the PIs, Sponsor Medical Monitor, and (if needed) a statistician, will be established under a charter to oversee the safety aspects of the study, and to render dose escalation/de-escalation decisions. Specifically, the SRC will perform ongoing review and adjudication of SAEs and other safety trends throughout the conduct of the study. The SRC membership will consist of the Sponsor's Medical Monitor and the Principal Investigator (or clinically qualified designee) from each active clinical site contributing patients to that cohort. The SRC is the final arbiter in the assessment of suspected DLTs. The SRC will assess the safety data arising from the trial prior to each dose escalation to determine whether the study will proceed to the next dose group, and establishes the infusion dose and administration time and pattern (such as priming dose, intermittent administration, etc.) for the next upcoming cohort. The SRC may also advise on changes in recommended pre-medication levels and concomitant medication allowances as needed. For single-patient cohorts, the SRC will only be required to convene prior to a cohort dose escalation if a suspected DLT is reported in a cohort or another emergent meaningful safety finding is apparent. If not, Email communicated is acceptable. All SRC-decisions will be documented in written minutes.

The tasks of the SRC are governed by a written SRC Charter.

The SRC established to oversee the safety aspects of the phase 1b portion of the study will consist, at a minimum, of the Sponsor's Medical Monitor, and the 2 Principal Investigators from each open 1b cohort. A statistician may be invited as needed. The phase 1b safety committee will convene at a minimum of every 6 months (or more frequently depending on enrollment or observed safety profile) and perform ongoing review of SAEs and other safety-related data throughout the conduct of the study.

9.2 Grading and Intensity of Adverse Events

The Investigator will grade the severity of each AE using, when applicable, the NCI CTCAE, version 5. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as mild, moderate, severe, life-threatening/debilitating, or fatal, as defined below.

- **Grade 1** – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2**– Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities Daily Living (ADL). **Grade 3** – Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 –Life-threatening consequences; urgent intervention indicated.
- Grade 5 –Death related to AE.

9.3 Causality assessment of Adverse Even

All clinical AEs and clinically significant abnormal laboratory values will be evaluated by the Principal Investigator for potential relationship to the investigational drug administration in the following categories:

• **Definitely Related:** An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.

• **Probably Related:** An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.

• **Possibly Related:** An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.

• **Unlikely Related:** An AE is unlikely related when the event may have a temporal relationship to the drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, comorbidity, or underlying disease provide plausible explanations.

• **Not Related:** The cause of the AE is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality, then the event must be assessed as possibly related to research participation and should be reported. Often, the cause of an unrelated AE is disease progression.

The event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting unless clearly and directly attributable to the underlying malignancy or known co-morbidity. The final determination of relatedness will be made by the Sponsor.

All drug related AEs must be followed until resolution or until no further improvement is expected.

The following factors should also be considered:

- Temporal sequence from treatment with the study drug.
- Preclinical and prior clinical data regarding whether a particular AE could be an effect of the study drug (or class of drug).
- Pharmacology and PK of the investigational product.

An unexpected AE is an experience not previously reported or an AE that occurs with specificity, severity, or frequency that is not consistent with the current PSB202 IB.

9.4 Serious Adverse Event Reporting

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of the informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

In the event of an accidental or intentional overdose by a patient, the site staff must immediately inform Parexel Clinical Safety. The eCRF must be updated to reflect this information. In the event that the overdose is associated with an SAE, the 2 events should be linked. In the event of an AE associated with an overdose, an SAE report form must be completed detailing the AE and the overdose details.

9.4.1 Serious Adverse Event Reporting – Procedures for Investigators: Initial Report

All SAEs occurring from the time informed consent is signed through 28 days after the last dose must be reported to Parexel Clinical Safety within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria).

All SAEs that the Investigator considers related to study drug occurring after the 28-day follow-up period must be reported to the Sponsor.

To report the SAE, complete the paper SAE form located in the Study Binder. Email the completed paper SAE form to Safety (email address is listed below) within 24 hours of awareness.

Safety Contact Information:

Parexel Clinical Safety

Parexel International Email:

GPPG_CNSY_Medical@parexel.com

The Investigator will be requested to supply detailed information regarding the event. SAEs must also be reported to the Institutional Review Board/ Independent Ethics Committee (IRB/IEC) and a copy of that report must be retained at the investigative site and filed in the Investigator Site File in accordance with the requirements of that institution.

Although not considered an AE per se, the Sponsor must be notified of any patient or patient’s partner who becomes pregnant during a clinical study.

9.5 Serious Adverse Event Follow-up

For all SAEs occurring during the study, the Investigator must submit follow-up reports to the Sponsor regarding the status of the SAE and the patient's subsequent course until the SAE has resolved, or until the condition stabilizes or is deemed chronic (in the case of persistent impairment), or the patient dies.

9.6 Pregnancy Reporting

If the patient or partner of a patient participating in the study becomes pregnant during the study or within 28 days of discontinuing study drug, the Investigator should report the pregnancy to Parexel Clinical Safety within 24 hours of being notified. Parexel Clinical Safety will then forward the Exposure In Utero form to the Investigator for completion.

A patient becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The patient or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify Parexel Clinical Safety. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

10 STUDY ADMINISTRATION

10.1 Regulatory and Ethical Considerations

10.1.1 Regulatory Authority Approval

This study will be conducted in accordance with the standard of International Conference on Harmonisation-Good Clinical Practice (ICH GCP), an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human patients. All applicable country and local regulations will also be observed. Compliance with these standards provides assurance that the rights, safety, and well-being of study patients are protected, consistent with the principles in the Declaration of Helsinki, and that the clinical study data are credible.

10.1.2 Ethics Approval

It is the responsibility of the Investigator to ensure that the appropriate IRB/IEC has reviewed and approved this protocol prior to initiating the study. The Investigator must provide the Sponsor or Sponsor's representative with current and revised IRB/IEC membership rosters that include the members' occupations and qualifications. Sites within the United States (US) may provide a copy of the US Department of Health and Human Services Assurance Number.

The IRB/IEC must also review and approve the clinical site's ICF, other written information provided to the patient, and all advertisements that may be used for patient recruitment. The Investigator will provide the study monitor with copies of these documents and of dated IRB/IEC approval(s) prior to the start of the study.

If the protocol or the ICF is amended during the study, the Investigator is responsible for ensuring that the IRB/IEC has reviewed and approved these amended documents. Approval of the amended documents must be obtained from the IRB/IEC before implementation and before new patients are consented to participate in the study using the amended version of the ICF. The Investigator must provide the Sponsor with the dated IRB/IEC approval of the amended documents as soon as available.

10.1.3 Patient Informed Consent

Prior to study entry, the Investigator or designee will explain the nature, purpose, benefits, and risks of participation in the study to each patient, patient's legally acceptable representative, or impartial witness. Written informed consent must be obtained prior to the patient entering the study (before initiation of any study-related screening procedure). Sufficient time will be allowed to discuss any questions raised by the patient. The ICF, which will contain all US federally-required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act authorization information in a language that is understandable to the patient, must be signed by all patients. The process of obtaining

consent will be in compliance with all applicable local and country regulations and ICH requirements.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to IRB/IEC approval of the amended form. The clinical site must use the amended ICF for all new patients and must re-consent any ongoing patients with the amended ICF, if instructed to do so by the IRB/IEC.

The sample ICF prepared by the Sponsor may be found in the Study Manual. The consent and re-consenting process should be properly documented in the source documentation.

10.1.4 Serious Adverse Event Notification to the Institutional Review Board/Independent Ethics Committee

Suspected unexpected serious adverse reactions (SUSARs) will be reported to the IRB/IEC according to their institutional policy by the Investigator or Sponsor (or Sponsor designee) according to country requirements. Copies of each report and documentation of IRB/IEC notification and acknowledgement of receipt will be kept in the Investigator's study file.

10.1.5 Sponsor Safety Reporting to Regulatory Authorities

The Sponsor or its representative is required to report certain study events in an expedited manner to the Food and Drug Administration, the European Medicines Agency's Eudra Vigilance electronic system according to Directive 2001/20/EC (in case the study opens in Europe), and to all country Regulatory Authorities where the study is being conducted, according to local applicable regulations.

The following describes the safety reporting timeline requirements for SUSARs and other reportable events:

Immediately and within 7 calendar days:

- Any suspected adverse event that is associated with the use of the study drug, unexpected, and fatal or life-threatening. Follow-up information must be reported in the following 8 days.

Immediately and within 15 calendar days:

- Any suspected adverse event that is associated with the use of the study drug, unexpected, and serious, but not fatal or life-threatening, and there is evidence to suggest a causal relationship between the study drug and the event.
- Any finding from tests in laboratory animals that suggest a significant risk for human patients, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any event in connection with the conduct of the study or the development of the study drug that may affect the safety of the study patients. In addition, periodic safety reporting to regulatory authorities will be performed by the Sponsor or its representative according to national and local regulations.

10.2 Data Management

Source documents will be maintained by sites and used to enter data and complete the eCRFs in the clinical database (EDC or Clinical Data Management System [CDMS]). The Sponsor's monitors will routinely review the source documentation and verify the corresponding data entered on eCRFs in the clinical database. All entered, changed, and final data shall be available with a validated audit trail report or data extract report. The eCRFs shall be considered complete when all expected data has been entered and all discrepancies have been resolved or documented.

The Investigator must sign all eCRFs according to the EDC (CDMS) requirements.

10.3 Study Monitoring

Prior to the start of the study, the Sponsor's monitor will contact the clinical site to discuss the protocol and data collection procedures and conduct applicable training of site personnel. The Sponsor and its designees will also periodically contact the clinical site during the conduct of the study (which will include on-site visits) in accordance with applicable regulations and GCP. During these contacts, the monitoring activities will include:

- Checking and assessing the progress of the study.
- Reviewing study data collected to date for completeness and accuracy.
- Conducting source document verifications by reviewing each patient's eCRF against source documents.
- Identifying any issues and addressing resolutions.
- Recording and reporting protocol deviations not previously reported to the Sponsor.
- Confirming that SAEs have been properly reported to the Sponsor and submitted to the IRB/IEC if appropriate.

These activities will be done in order to verify that the data are authentic, accurate, and complete; that the safety and rights of the patient are being protected; and that the study is conducted in accordance with the currently approved protocol, ICH GCP, and all applicable regulatory requirements. Additionally, to ensure compliance with ICH GCP and all applicable regulatory requirements, the Sponsor or designee may conduct a quality assurance audit.

10.4 Termination

Upon completion of the study, the following activities, when applicable, must be conducted by the site monitor and the Investigator:

- Submission of all study data to the Sponsor.
- Completion of all data clarifications and/or resolutions.

- Reconciliation and final disposition of investigational product.
- Review of site study files for completeness.

In addition, the Sponsor reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform the Investigator and will also inform the IRB/IEC with the reasons for the action. In the event of prematurely termination, all study data must be submitted to the Sponsor. In addition, the clinical site must document final disposition of all unused investigational product in accordance with the Sponsor's procedures.

10.5 Records Retention

Patient records, source documents, monitoring visit logs, investigational product inventory, regulatory documents, and other correspondence pertaining to the study must be maintained in the appropriate site study files according to ICH GCP and applicable regulatory requirement(s). These records will be retained for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing.

10.6 Confidentiality of Information

Patient names will remain confidential and will not be supplied to the Sponsor or its designee. The Investigator will maintain a personal patient identification list (patient and treatment numbers with the corresponding patient names) to enable records to be identified.

11 APPENDICES

Appendix A Prior CD20+ directed antibodies, radio-immunotherapy, and prior BTK Inhibitors (Examples)

This list represents the names of certain known prior non-chemotherapy treatments for B-cell malignancy; the list includes both marketed and development-stage compounds. Prior treatment and relapse following treatment with any of the compounds listed below qualifies as a prior line of treatment per protocol. The list below is not an exclusionary list, but an inclusionary list. Compounds belonging to different drug-classes (PI3-kinase inhibitors, BCL2 inhibitors etc.) may also count towards qualifying prior therapy.

Prior CD20+ targeting antibodies and radio-immunotherapy used in the treatment of certain NHL and/or CLL/SLL include:

- Rituximab
- Obinituzumab
- Ofatumumab
- Ublituximab
- Y^{90} Ibritumomab tiuxetan

Prior BTK inhibitors used in the treatment of CLL/SLL or certain NHL include:

- Acalabrutinib
- ARQ-531
- GDC-0853
- Ibrutinib
- TG-1701
- Vecabrutinib (SNS-062)
- Zanubrutinib (BGB-3111)
- LOXO-305

Appendix B Treatment Failure and Intolerance

Treatment Failure:

Relapse: evidence of disease progression according to disease-defined criteria in a patient who has previously achieved a complete response (CR/CRi) or partial response (PR) for ≥6 months

Refractory disease: treatment failure as defined by less than CR or PR (i.e., stable disease [SD], nonresponse, progressive disease, [PD] death from any cause) or progression within 6 months from the last dose of therapy.

Treatment Intolerance:

- ≥1 Grade 3 or ≥2 Grade 2 non-hematologic toxicities or
- ≥1 Grade 3 neutropenia with infection or fever or
- ≥1 Grade 4 hematologic toxicity
- the above leads to treatment discontinuation for ≥14 days without disease progression (patient could have progressed after 14 days)
- Toxicities should resolve to ≤Grade 1 off therapy

References:

(Hallek, Cheson et al. 2018, Mato et al., 2018)

Appendix C Chronic Lymphocytic Leukemia Response Assessment (iwCLL)

Parameter	CR*	PR*	Partial Response With Lymphocytosis:	Progressive Disease*
Group A				
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or new lesion
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi.	50% reduction in marrow infiltrate, or B-lymphoid nodules	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B				
Platelet count	> 100,000/μL	> 100,000/μL or increase ≥ 50% over baseline	> 100,000/μL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/μL	> 1,500/μL or > 50% improvement over baseline	> 1,500/μL or > 50% improvement over baseline	

Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete remission (response); CRi, CR with incomplete bone marrow recovery; CT, computed tomography; PD, disease progression; PR, partial remission (response); SD, stable disease.

Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).

CR*: all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR*: at least two of the criteria of group A (lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes) plus one of the criteria of Group B (platelets, hemoglobin, or neutrophils) have to be met; partial response with lymphocytosis: presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for platelets, hemoglobin, or neutrophils have to be met; SD: is absence of progressive disease and failure to achieve at least a PR; progressive disease: at least one of the above progressive disease criteria has to be met.
Note: Isolated elevation of treatment-related lymphocytosis by itself will not be considered PD unless patient becomes symptomatic from this per Cheson, 2012.

a. Computed tomography (CT) scan of abdomen, pelvis, and thorax may be used if previously abnormal
b. Without need for exogenouse growth factors
c. In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

† Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination)
‡ These parameters are irrelevant for some response categories

Note: Temporary withholding of study drug (eg, for drug-related toxicity, surgery, or intercurrent illness) for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. In such circumstances, and if medically appropriate, patients may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be performed to document whether tumor control can be maintained or whether actual disease progression has occurred.

Appendix D Waldenström Macroglobulinemia Response Assessment (iwWM)

Response Category	Description
Complete Response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response (VGPR)	Monoclonal IgM protein is detectable ≥ 90% reduction in serum IgM level from baseline[a] Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial Response (PR)	Monoclonal IgM protein is detectable ≥ 50% but < 90% reduction in serum IgM level from baseline[a] Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor Response (MR)	Monoclonal IgM protein is detectable ≥ 25% but < 50% reduction in serum IgM level from baseline[a] No new signs or symptoms of active disease
Stable Disease (SD)	Monoclonal IgM protein is detectable < 25% reduction and < 25% increase in serum IgM level from baseline[a] No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Progressive Disease (PD)	≥ 25% increase in serum IgM level[a,b] from lowest nadir (requires confirmation) and/or progression in clinical features attributable to the disease

Source: Anderson, J Natl Compr Canc Netw 2012; 10: 1211-9.

a. Sequential changes in IgM levels may be determined by either M-protein quantitation by densitometry or total serum IgM quantitation by nephelometry.
b. An absolute increase of >5 G/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion.

Appendix E Lugano Classification of Response in Non-Hodgkin's Lymphoma

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to <1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following):**
Partial Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	>50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation Absent/normal, regressed, but no increase

Response and Site	PET-CT–Based Response	CT-Based Response
		Spleen must have regressed by >50% in length beyond normal
Nonmeasured lesions	Not applicable	
Organ enlargement	Not applicable	
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow, but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease** requires at least 1 of the following PPD progression:
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	An individual node/lesion must be abnormal with: LDi>1.5 cm and
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Increase by >50% from PPD nadir and An increase in LDi or

Response and Site	PET-CT–Based Response	CT-Based Response
		SDi from nadir 0.5 cm for lesions <2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly New or clear progression of preexisting nonmeasured lesions
Nonmeasured lesions	None	Regrowth of previously resolved lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	A new node _ 1.5 cm in any axis A new extranodal site _ 1.0 cm in any axis; if _ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS = 5-point scale; CT = computed tomography; FDG = fluorodeoxyglucose; GI = gastrointestinal; IHC = immunohistochemistry; LDi = longest transverse diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

Footnotes: *A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability, but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with

measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging.

In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake >mediastinum, but ≤liver; 4, uptake moderately >liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma. Source: (Cheson, Fisher et al. 2014).

Appendix F Guidelines for Patient Sample Collection for Central Analysis (Phase 1b only)

Select patient samples form peripheral blood, bone marrow and/or nodal/extranodal sites will be collected during the conduct of this study for central assessment of biomarker status, laboratory tests required for disease response evaluation and corelative studies. The following table is meant to be a guide; refer to the Laboratory Manual for additional details. [1] indicates requirement for local collection and assessment as well (optional for MRD assessment); for CLL patients, when cfDNA is collected, blood samples will also be collected for PBMC and CD19+ cell isolation.

Tumor Type	Time Point	Peripheral Blood	Bone Marrow	Lymph Node/Tumor Tissue
CLL	Baseline	• Required, used for: • CBC, lymphocyte subsets, B-cell count[1] • MRD[1] • cfDNA, • Optional for PK-PD	• Required unless available after last treatment and performed within 90 days	• Required **only** if unable to detect disease in the blood or bone marrow
	Response time points	• Required, used for: • CBC, lymphocyte subsets, B-cell count[1] • MRD[1] • cfDNA, • Optional for PK-PD	• Required at CR/PR[1]	
	Progression	• Required, used for: • CBC, lymphocyte subsets, B-cell count[1] • cfDNA • Optional for PK-PD	• Optional	• Optional
WM	Baseline	• SPEP/IF/FLC/quantitative Igs[1] • cfDNA	• Required unless available after last treatment and performed within 90 days	• Required **only** if unable to detect disease in the blood or bone marrow

	Response time points	• SPEP/IF/FLC/quantitative Igs[1] • cfDNA	• Required at CR/PR[1]	
	Progression	• SPEP/IF/FLC/quantitative Igs[1] • cfDNA	• Optional	• Optional
MCL	Baseline	• cfDNA	• Required unless available after last treatment and performed within 90 days	• Required archived or fresh at baseline
	Response time points	• cfDNA		
	Progression	• cfDNA	• Optional	• Optional
Other NHL (e.g. MZL, FL, DLBCL)	Baseline	• cfDNA		• Required archived or fresh at baseline
	Response time points	• cfDNA	Required at CR/PR only if known disease involvement at baseline	
	Progression	• cfDNA	• Optional	•Optional

Appendix G Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix H PK-sampling schedule for clinics/subjects who opt into participation in "Intense PK".

Table 1a. Phase 1a PK-sampling schedule for cohorts with the first full cohort designated dose of PSB202 on C1D8

Cycle	Day		Timepoint	PK
C1	D1 Priming dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
	D8 Targeted dose	Pre-dose	Within 30 min	●
		Post dose	2 h±15 min	●
			4 h±15 min	●
			8 h±1h	●
	D9		24 h±3 h	●
	D10		48 h±6 h	●
	D11		72 h±9 h	●
	D13		120 h±15 h	●
	D15 Targeted dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
C4	D1	Pre-dose	Within 30 min	●
		Post dose	2 h±15 min	●
			4 h±15 min	●
			8 h±1h	●
	D2		24 h±3h	●
	D3		48 h±6 h	●
	D6		120 h±15 h	●
	D8		168 h±20 h	●
	D15		336h±42 h	●
C2, C3, C5, C6	D1	Pre-dose	Within 30 min	●
EOT				●

Table 1b. Phase 1a PK-sampling schedule for cohorts with the first full dose of PSB202 on C1D15

Cycle	Day		Timepoint	PK
C1	D1 Priming dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
	D8 Priming dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
	D15 Targeted dose	Pre-dose	Within 30 min	●
		Post dose	2 h ±15 min	●
			4 h ±15 min	●
			8 h ±1h	●
			24 h ±3h	●
			48 h ±6 h	●
			72 h ±9 h	●
			120 h ±15 h	●
C4	D1	Pre-dose	Within 30 min	●
		Post dose	2 h ±15 min	●
			4 h ±15 min	●
			8 h ±1h	●
	D2		24 h ±3h	●
	D3		48 h ±6 h	●
	D6		120 h ±15 h	●
	D8		168 h ±20 h	●
	D15		336h ±42 h	●
C2, C3, C5, C6	D1	Pre-dose	Within 30 min	●
EOT				●

Table 1c. Phase 1a PK-sampling schedule for cohorts with the first full dose of PSB202 on C2D1

Cycle	Day		Timepoint	PK
C1	D1 Priming dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
	D8 Priming dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
	D15 Targeted dose	Pre-dose	Within 30 min	●
		Post dose	4 h ±15 min	●
C2	D1	Pre-dose	Within 30 min	●
		Post dose	2 h ±15 min	●
			4 h ±15 min	●
			8 h ±1h	●
	D2		24 h ±3h	●
	D3		48 h ±6 h	●
	D6		120 h ±15 h	●
	D8		168 h ±20 h	●
	D15		336h ±42 h	●
C4	D1	Pre-dose	Within 30 min	●
		Post dose	2 h ±15 min	●
			4 h ±15 min	●
			8 h ±1h	●
	D2		24 h ±3h	●
	D3		48 h ±6 h	●
	D6		120 h ±15 h	●
	D8		168 h ±20 h	●
	D15		336h ±42 h	●
C3, C5, C6	D1	Pre-dose	Within 30 min	●
EOT				●

Table 2. Phase 1b PK-sampling schedule

Cycle	Day		Timepoint	PK
C1	D1	Pre-dose	Within 30 min	●
		End of infusion	Within 15min	●
	D8	Pre-dose	Within 30 min	●
		End of infusion	Within 15min	●
	D15	Pre-dose	Within 30 min	●
		End of infusion	Within 15min	●
C2	C2D1	Pre-dose	Within 30 min	●
	C2D1	Post dose	Within 15min	●
			2 h ±15 min	●
			4 h ±15 min	●
			8 h ±1 h	●
	C2D2		24 h ±3h	●
	C2D4		48 h ±9 h	●
	C2D6		120 h ±15 h	●
	C2D8		168 h ±20 h	●
	C2D15		336h ±42 h	●
C4，C6 and C8	D1	Pre-dose	Within 30 min	●
EOT				●

Appendix I. IWCLL criteria for hematologic toxicity of CLL

Evaluation of treatment-related toxicity requires careful consideration of both the manifestations of the underlying disease and the anticipated adverse reactions to the agents used in therapy. Because many CLL patients then would be considered to have grade 2 to 4 hematological toxicity at the initiation of treatment.
Furthermore, the absolute blood neutrophil counts are rarely used at the initiation of therapy to modify the treatment dose because these values typically are unreliable in CLL patients with lymphocytosis.

Grade criteria for hematologic toxicity of CLL

Grade	Decrease in PLT[a] or Hb[b] (nadir) from baseline value, %	Absolute neutrophil count[c] (nadir） $\times 10^9$/L
0	No change to 10	≥ 2
1	11 - 24	≥ 1 and <2
2	25 – 49	≥ 1 and <1
3	50 - 74	≥ 0.5 and <1
4	≥ 75	< 0.5
• Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.		

a. Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is 20, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
b. Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
c. If the absolute neutrophil count (ANC) reaches 1, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was 1 before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity, but should be documented.

References:

Hallek, M et al. iwCLL guideline 2018. Blood (2018) 131 (25): 2745–2760.

12 REFERENCES

Aaronson, N. K., S. Ahmedzai, B. Bergman, M. Bullinger, A. Cull, N. J. Duez, A. Filiberti, H. Flechtner, S. B. Fleishman, J. C. de Haes and et al. (1993). "The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology." J Natl Cancer Inst **85**(5): 365-376.

Barr, P. M., J. R. Brown, P. Hillmen, S. O'Brien, J. C. Barrientos, N. M. Reddy, S. Coutre, S. P. Mulligan, U. Jaeger, R. R. Furman, F. Cymbalista, M. Montillo, C. Dearden, T. Robak, C. Moreno, J. M. Pagel, J. A. Burger, S. Suzuki, J. Sukbuntherng, G. Cole, D. F. James and J. C. Byrd (2017). "Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL." Blood **129**(19): 2612-2615.

Bonfiglio, S., Scarfo, L., Gaidano, G., Trentin, L. BOnello, L., Panayiotidis, P., Reda, G., Forconi, F., Stavroyianni, N., Tam, C., Coscia, M., RIngshausen, I., Jaksic, O., Davis, Z., Pavlovsky, C., Capasso, A., Ranghetti, P., Cortese, D., Skaftason, A., Stamatopoulos, K., Rosenquist, R., Ghia, P. (2018). "HALF OF CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS RELAPSING UNDER IBRUTINIB CARRY BTK AND PLCG2 MUTATIONS: A EUROPEAN RESEARCH INITIATIVE ON CLL (ERIC) REAL-WORLD STUDY." European Hematology Association Anuual Meeting **Abstract LB 2601**.

Byrd, J. C., J. R. Brown, S. O'Brien, J. C. Barrientos, N. E. Kay, N. M. Reddy, S. Coutre, C. S. Tam, S. P. Mulligan, U. Jaeger, S. Devereux, P. M. Barr, R. R. Furman, T. J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S. J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J. J. Jones, A. D. Chu, M. Fardis, J. McGreivy, F. Clow, D. F. James, P. Hillmen and R. Investigators (2014). "Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia." N Engl J Med **371**(3): 213-223.

Byrd, J. C., R. R. Furman, S. E. Coutre, I. W. Flinn, J. A. Burger, K. A. Blum, B. Grant, J. P. Sharman, M. Coleman, W. G. Wierda, J. A. Jones, W. Zhao, N. A. Heerema, A. J. Johnson, J. Sukbuntherng, B. Y. Chang, F. Clow, E. Hedrick, J. J. Buggy, D. F. James and S. O'Brien (2013). "Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia." N Engl J Med **369**(1): 32-42.

Byrd, J. C., B. Harrington, S. O'Brien, J. A. Jones, A. Schuh, S. Devereux, J. Chaves, W. G. Wierda, F. T. Awan, J. R. Brown, P. Hillmen, D. M. Stephens, P. Ghia, J. C. Barrientos, J. M. Pagel, J. Woyach, D. Johnson, J. Huang, X. Wang, A. Kaptein, B. J. Lannutti, T. Covey, M. Fardis, J. McGreivy, A. Hamdy, W. Rothbaum, R. Izumi, T. G. Diacovo, A. J. Johnson and R. R. Furman (2016). "Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia." N Engl J Med **374**(4): 323-332.

Byrd JC, Pagel JM, Awan FT, et al. (2014). A phase 1 study evaluating the safety and tolerability of otlertuzumab, an anti-CD37 mono-specific ADAPTIR therapeutic protein in chronic lymphocytic leukemia. Blood **123**(9): 1302-1308).

Chang, B. Y., M. Francesco, M. F. De Rooij, P. Magadala, S. M. Steggerda, M. M. Huang, A. Kuil, S. E. Herman, S. Chang, S. T. Pals, W. Wilson, A. Wiestner, M. Spaargaren, J. J. Buggy and L. Elias (2013). "Egress of CD19(+)CD5(+) cells into peripheral blood following treatment with the Bruton tyrosine kinase inhibitor ibrutinib in mantle cell lymphoma patients." Blood **122**(14): 2412-2424.

Cheson, B. D., R. I. Fisher, S. F. Barrington, F. Cavalli, L. H. Schwartz, E. Zucca, T. A. Lister, A. L. Alliance, G. Lymphoma, G. Eastern Cooperative Oncology, C. European Mantle Cell Lymphoma, F. Italian Lymphoma, R. European Organisation for, G. Treatment of Cancer/Dutch Hemato-Oncology, O. Grupo Espanol de Medula, G. German High-Grade Lymphoma Study, G. German Hodgkin's Study, G. Japanese Lymphorra Study, A. Lymphoma Study, N. C. T. Group, G. Nordic Lymphoma Study, G. Southwest Oncology and I. United Kingdom National Cancer Research (2014). "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification." J Clin Oncol **32**(27): 3059-3068.

Chiron, D., M. Di Liberto, P. Martin, X. Huang, J. Sharman, P. Blecua, S. Mathew, P. Vijay, K. Eng, S. Ali, A. Johnson, B. Chang, S. Ely, O. Elemento, C. E. Mason, J. P. Leonard and S. Chen-Kiang (2014). "Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma." Cancer Discov **4**(9): 1022-1035.

CTFG, C. T. F. G. (2014). "Recommendations related to contraception and pregnancy testing in clinical trials ".

Deckert, J., P. U. Park, S. Chicklas, M. Yi, K. C. Lai, M. Mayo, C. N. Carrigan, H. K. Erickson, J. Iinkas, R. J. Lutz, T. Chittenden, and J. M. Lambert (2013). "A novel anti-CD37 antibody-drug conjugate with multiple anti-tumor mechanisms for the treatment of B-cell malignancies." Blood **122**(20): 3500-3510.

Hallek, M., B. D. Cheson, D. Catovsky, F. Caligaris-Cappio, G. Dighiero, H. Dohner, P. Hillmen, M. Keating, E. Montserrat, N. Chiorazzi, S. Stilgenbauer, K. R. Rai, J. C. Byrd, B. Eichhorst, S. O'Brien, T. Robak, J. F. Seymour and T. J. Kipps (2018). "iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL." Blood **131**(25): 2745-2760.

Hendriks, R. W., R. G. Bredius, K. Pike-Overzet and F. J. Staal (2011). "Biology and novel treatment options for XLA, the most common monogenetic immunodeficiency in man." Expert Opin Ther Targets **15**(8): 1003-1021.

Herman, S. E., A. L. Gordon, E. Hertlein, A. Ramanunni, X. Zhang, S. Jaglowski, J. Flynn, J. Jones, K. A. Blum, J. J. Buggy, A. Hamdy, A. J. Johnson and J. C. Byrd (2011). "Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765." Blood **117**(23): 6287-6296.

Jones, J. A., A. R. Mato, W. G. Wierda, M. S. Davids, M. Choi, B. D. Cheson, R. R. Furman, N. Lamanna, P. M. Barr, L. Zhou, B. Chyla, A. H. Salem, M. Verdugo, R. A. Humerickhouse, J. Potluri, S. Coutre, J. Woyach and J. C. Byrd (2018). "Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial." Lancet Oncol **19**(1): 65-75.

Kamel, S., L. Horton, L. Ysebaert, M. Levade, K. Burbury, S. Tan, M. Cole-Sinclair, J. Reynolds, R. Filshie, S. Schischka, A. Khot, S. Sandhu, M. J. Keating, H. Nandurkar and C. S. Tam (2015). "Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation." Leukemia **29**(4): 783-787.

Kil, L. P., M. J. de Bruijn, J. A. van Hulst, A. W. Langerak, S. Yuvaraj and R. W. Hendriks (2013). "Bruton's tyrosine kinase mediated signaling enhances leukemogenesis in a mouse model for chronic lymphocytic leukemia." Am J Blood Res **3**(1): 71-83.

Leblond, V., E. Kastritis, R. Advani, S. M. Ansell, C. Buske, J. J. Castillo, R. Garcia-Sanz, M. Gertz, E. Kimby, C. Kyriakou, G. Merlini, M. C. Minnema, P. Morel, E. Morra, M. Rummel, A. Wechalekar, C. J. Patterson, S. P. Treon and M. A. Dimopoulos (2016). "Treatment recommendations from the Eighth International Workshop on Waldenstrom's Macroglobulinemia." Blood **128**(10): 1321-1328.

Mato, A. R., C. Nabhan, P. M. Barr, C. S. Ujjani, B. T. Hill, N. Lamanna, A. P. Skarbnik, C. Howlett, J. J. Pu, A. R. Sehgal, L. E. Strelec, A. Vandegrift, D. M. Fitzpatrick, C. S. Zent, T. Feldman, A. Goy, D. F. Claxton, S. H. Bachow, G. Kaur, J. Svoboda, S. D. Nasta, D. Porter, D. J. Landsburg, S. J. Schuster, B. D. Cheson, P. Kiselev and A. M. Evens (2016). "Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience." Blood **128**(18): 2199-2205.

Mato, A. R., C. Nabhan, M. C. Thompson, N. Lamanna, D. M. Brander, B. Hill, C. Howlett, A. Skarbnik, B. D. Cheson, C. Zent, J. Pu, P. Kiselev, A. Goy, D. Claxton, K. Isaac, K. H. Kennard, C. Timlin, D. Landsburg, A. Winter, S. D. Nasta, S. H. Bachow, S. J. Schuster, C. Dorsey, J. Svoboda, P. Barr and C. S. Ujjani (2018). "Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis." Haematologica **103**(5): 874-879.

Mato, A. R. S., S.J.; Lamanna, N.; Filinn, I.W.; Barrientos, J.; (2018). "A PHASE 2 STUDY TO ASSESS THE SAFETY AND EFFICACY OF UMBRALISIB (TGR-1202) IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WHO ARE INTOLERANT TO PRIOR BTK OR PI3K DELTA INHIBITOR THERAPY." European Hematology Association Annual Meeting **Abstract S808**.

McMullen, J. R., E. J. Boey, J. Y. Ooi, J. F. Seymour, M. J. Keating and C. S. Tam (2014). "Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling." Blood **124**(25): 3829-3830.

Noy, A., S. de Vos, C. Thieblemont, P. Martin, C. R. Flowers, F. Morschhauser, G. P. Collins, S. Ma, M. Coleman, S. Peles, S. Smith, J. C. Barrientos, A. Smith, B. Munneke, I. Dimery, D. M. Beaupre and R. Chen (2017). "Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma." Blood **129**(16): 2224-2232.

Rawlings, D. J., D. C. Saffran, S. Tsukada, D. A. Largaespada, J. C. Grimaldi, L. Cohen, R. N. Mohr, J. F. Bazan, M. Howard, N. G. Copeland and et al. (1993). "Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice." Science **261**(5119): 358-361.

Robak T, Hellmann A, Kloczko J, et al. (2016). Randomized phase 2 study of otlertuzumab and bendamustine versus bendamustine in patients with relapsed chronic lymphocytic leukaemia. Brit J Hematol **176**: 618-628.

Sato, R., J. Jacob and S. Gaballa (2018). "Rapid flare of immune thrombocytopenia after stopping ibrutinib in a patient with chronic lymphocytic leukemia." Leukemia & Lymphoma **59**(7): 1738-1741.

Schemper, M. and T. L. Smith (1996). "A note on quantifying follow-up in studies of failure time." Control Clin Trials **17**(4): 343-346.

Shanafelt, T. D., B. J. Borah, H. D. Finnes, K. G. Chaffee, W. Ding, J. F. Leis, A. A. Chanan-Khan, S. A. Parikh, S. L. Slager, N. E. Kay and T. G. Call (2015). "Impact of Ibrutinib and Idelalisib on the Pharmaceutical Cost of Treating Chronic Lymphocytic Leukemia at the Individual and Societal Levels." Journal of Oncology Practice **11**(3): 252-258.

Stilgenbauer S, Schleinitz T, Eichhorst B, **et** al. (2019). Phase 1 first-in-human trial of the anti-CD37 antibody BI 836826 in relapsed/refractory chronic lymphocytic leukemia. Leukemia **33**(10): 2531-2535.

Tam, C., A. P. Grigg, S. Opat, M. Ku, M. Gilbertson, M. A. Anderson, J. F. Seymour, D. S. Ritchie, C. Dicorleto, B. Dimovski, E. Hedrick, J. Yang, L. Wang, L. Luo, L. Xue and A. W. Roberts (2015). "The BTK Inhibitor, Bgb-3111, Is Safe, Tolerable, and Highly Active in Patients with Relapsed/ Refractory B-Cell Malignancies: Initial Report of a Phase 1 First-in-Human Trial." Blood **126**(23): 832-832.

Thomas, J. D., P. Sideras, C. I. Smith, I. Vorechovsky, V. Chapman and W. E. Paul (1993). "Colocalization of X-linked agammaglobulinemia and X-linked immunodeficiency genes." Science **261**(5119): 355-358.

Treon, S. P., C. K. Tripsas, K. Meid, D. Warren, G. Varma, R. Green, K. V. Argyropoulos, G. Yang, Y. Cao, L. Xu, C. J. Patterson, S. Rodig, J. L. Zehnder, J. C. Aster, N. L. Harris, S.

Kanan, I. Ghobrial, J. J. Castillo, J. P. Laubach, Z. R. Hunter, Z. Salman, J. Li, M. Cheng, F. Clow, T. Graef, M. L. Palomba and R. H. Advani (2015). "Ibrutinib in previously treated Waldenstrom's macroglobulinemia." N Engl J Med **372**(15): 1430-1440.

Turtle, C. J., K. A. Hay, L.-A. Hanafi, D. Li, S. Cherian, X. Chen, B. Wood, A. Lozanski, J. C. Byrd, S. Heimfeld, S. R. Riddell and D. G. Maloney (2017). "Durable Molecular Remissions in Chronic Lymphocytic Leukemia Treated With CD19-Specific Chimeric Antigen Receptor–Modified T Cells After Failure of Ibrutinib." Journal of Clinical Oncology **35**(26): 3010-3020.

U.S.-Food-and-Drug-Administration (2007). "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics ".

US-FDA (2005). "Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005).".

Vetrie, D., I. Vorechovsky, P. Sideras, J. Holland, A. Davies, F. Flinter, L. Hammarstrom, C. Kinnon, R. Levinsky, M. Bobrow and et al. (1993). "The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases." Nature **361**(6409): 226-233.

Vogel, W. H. (2010). "Infusion reactions: diagnosis, assessment, and management." Clin J Oncol Nurs. 14(2): E10-21

Wang, M. L., S. Rule, P. Martin, A. Goy, R. Auer, B. S. Kahl, W. Jurczak, R. H. Advani, J. E. Romaguera, M. E. Williams, J. C. Barrientos, E. Chmielowska, J. Radford, S. Stilgenbauer, M. Dreyling, W. W. Jedrzejczak, P. Johnson, S. E. Spurgeon, L. Li, L. Zhang, K. Newberry, Z. Ou, N. Cheng, B. Fang, J. McGreivy, F. Clow, J. J. Buggy, B. Y. Chang, D. M. Beaupre, L. A. Kunkel and K. A. Blum (2013). "Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma." N Engl J Med **369**(6): 507-516.

Wang, T., D. Jacobson-Kram, A. M. Pilaro, D. Lapadula, A. Jacobs, P. Brown, J. Lipscomb and W. D. McGuinn (2010). "ICH guidelines: inception, revision, and implications for drug development." Toxicol Sci **118**(2): 356-367.

Woyach, J. A., R. R. Furman, T. M. Liu, H. G. Ozer, M. Zapatka, A. S. Ruppert, L. Xue, D. H. Li, S. M. Steggerda, M. Versele, S. S. Dave, J. Zhang, A. S. Yilmaz, S. M. Jaglowski, K. A. Blum, A. Lozanski, G. Lozanski, D. F. James, J. C. Barrientos, P. Lichter, S. Stilgenbauer, J. J. Buggy, B. Y. Chang, A. J. Johnson and J. C. Byrd (2014). "Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib." N Engl J Med **370**(24): 2286-2294.

Woyach, J. A., A. S. Ruppert, D. Guinn, A. Lehman, J. S. Blachly, A. Lozanski, N. A. Heerema, W. Zhao, J. Coleman, D. Jones, L. Abruzzo, A. Gordon, R. Mantel, L. L. Smith, S. McWhorter, M. Davis, T. J. Doong, F. Ny, M. Lucas, W. Chase, J. A. Jones, J. M. Flynn, K. Maddocks, K. Rogers, S. Jaglowski, L. A. Andritsos, F. T. Awan, K. A. Blum, M. R. Grever,

G. Lozanski, A. J. Johnson and J. C. Byrd (2017). "BTK(C481S)-Mediated Resistance to Ibrutinib in Chronic Lymphocytic Leukemia." J Clin Oncol **35**(13): 1437-1443.

Xu, L., N. Tsakmaklis, G. Yang, J. G. Chen, X. Liu, M. Demos, A. Kofides, C. J. Patterson, K. Meid, J. Gustine, T. Dubeau, M. L. Palomba, R. Advani, J. J. Castillo, R. R. Furman, Z. R. Hunter and S. P. Treon (2017). "Acquired mutations associated with ibrutinib resistance in Waldenstrom macroglobulinemia." Blood **129**(18): 2519-2525.

Yang, G., Y. Zhou, X. Liu, L. Xu, Y. Cao, R. J. Manning, C. J. Patterson, S. J. Buhrlage, N. Gray, Y. T. Tai, K. C. Anderson, Z. R. Hunter and S. P. Treon (2013). "A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia." Blood **122**(7): 1222-1232.