12. Willing and able to provide written informed consent and comply with the requirements of the trial
13. CPK Grade < 2
14. Patients on a cholesterol lowering statin must be on a stable dose with no changes within 3 weeks prior to study start

Inclusion Criteria for Part B – PCNSL Expansion Cohorts of Combination Therapy:

1. Males and females ≥ 18 years of age
2. Life expectancy of at least 3 months
3. ECOG Performance Status of 0, 1, or 2
4. Histopathologically confirmed diagnosis of PCNSL (medical record is acceptable). Cerebral biopsies are not required if imaging reveals typical images of PCNSL
   a. Patients with parenchymal lesions must have unequivocal evidence (eg, presence of at least 1 bi-dimensionally measurable target lesion on brain magnetic resonance imaging (MRI) or head CT or a new lesion with CSF involvement) of disease progression on imaging within 28 days prior to Cycle 1 Day 1.
   b. For patients with leptomeningeal disease only, CSF cytology must document lymphoma cells or monotypic cells on flowcytometry, and/or imaging findings consistent with CSF disease within 28 days prior to Cycle 1 Day 1 (at the discretion of the Investigator).
5. Relapsed or refractory to a systemic frontline chemotherapy (eg, high-dose methotrexate-based therapies) AND no more than a total of 3 lines of prior anti-PCNSL therapies (patients with 4 prior lines of therapy may be allowed after consultation with the Sponsor Medical Monitor) AND the following:
   a. For Cohort 1, prior exposure to a Bruton tyrosine kinase (BTK) inhibitor alone or in combination is acceptable.
   b. For Cohort 2, must have direct progression on a BTK inhibitor (administered as monotherapy or in combination).
6. Patients must be able to tolerate gadolinium-enhanced MRI or contrast-enhanced CT
7. Patients must be able to tolerate lumbar punctures.
8. Acceptable organ function at Screening within 28-days prior to Cycle 1 Day 1 as described below:
   a. ANC ≥ 1,000/µL
   b. Platelet count ≥ 75,000/µL without transfusion
   c. Estimated creatinine clearance of ≥ 35 mL/min
   d. Hemoglobin ≥ 9.0 g/dL and without red blood cell (RBC) transfusion
   e. International normalized ratio (INR) ≤ 1.5 and activated partial thromboplastin time (aPTT) ≤ 1.5× ULN
   f. AST or ALT ≤ 2× ULN
   g. Total bilirubin ≤ 1.5× ULN or ≤ 3× ULN in patients with documented Gilbert's syndrome
9. CPK elevation < 2.5× ULN

10. For patients on a cholesterol lowering agent that has been associated with CPK elevations, such as statins or fibrates, the agent should be discontinued or replaced with an alternative if medically feasible. Otherwise, it should be reduced to the lowest dose that is biologically effective (ie, the lowest dose required to achieve the desired clinical effect).
11. Ability to swallow and retain oral medications
12. Negative serum pregnancy test in WOCP
13. WOCP and men who partner with a WOCP must agree to use highly effective contraceptive methods for the duration of the study and for 180 days after the last dose of study treatment.
14. Willing and able to provide written informed consent and comply with the requirements of the trial
15. Any toxicity caused by prior anti-cancer therapies must have recovered to Grade ≤1.

Exclusion Criteria for Parts A1 and A2 (Enrollment is Closed):

1. Patients with active CNS involvement other than PCNSL at study entry are ineligible. Patients with prior CNS disease (leptomeningeal disease or brain metastasis) that has been adequately treated (eg, radiation or intravenous or intrathecal chemotherapy) are permitted, but must have completed such treatment and have no evidence of active CNS disease for at least 4 weeks prior to the first dose of study treatment. Intrathecal chemoprophylaxis to prevent the emergence or recurrence of lymphoma in the CNS is permitted on study during dose expansion only and may be administered per institutional guidelines.
2. Radiotherapy delivered to non-target lesions involving > 25% of bone marrow within 1 week prior to starting study treatment or delivered to target lesions that will be followed on the study *NOTE: Prior sites of radiation will be recorded.*
3. *Exclusion criterion 3 was deleted as of protocol v5.0 (retained here to preserve numbering).*
4. Any prior systemic anti-cancer treatment such as chemotherapy, immunomodulatory drug therapy, etc., received within 14 days prior to the start of study treatment (with the exception of ibrutinib for Parts A2 and B, which may be continued as part of this study without interruption)
5. Current or planned glucocorticoid therapy, with the following exceptions:
   a. Doses ≤ 10 mg/day prednisolone or equivalent is allowed, provided that the steroid dose has been stable or tapering for at least 14 days prior to the first dose of study treatment.
   b. Inhaled, intranasal, intra-articular, and topical steroids are permitted.
6. Use of any investigational agent within 21 days or 5 half-lives, whichever is shorter, prior to start of study treatment
7. Presence of an acute or chronic toxicity resulting from prior anti-cancer therapy, with the exception of alopecia, that has not resolved to Grade ≤ 1, as determined by NCI CTCAE v4.03, within 7 days prior to the start of study treatment unless approved by the Medical Monitor
8. Known allergy or hypersensitivity to any component of the formulation of CA-4948 (or ibrutinib for entry into Parts A2 or B) used in this study

9. Major surgery, other than diagnostic surgery, < 28 days from the start of study treatment; minor surgery < 14 days from the start of study treatment

   NOTE: Insertion of a vascular access device is not considered minor surgery.

10. Known to be human immunodeficiency virus (HIV) positive or have an acquired immunodeficiency syndrome-related illness

11. Hepatitis B virus (HBV) DNA positive or hepatitis C virus (HCV) infection < 6 months prior to start of study treatment unless viral load is undetectable, or HCV with cirrhosis

    (*NOTE: testing required only in patients with history of HBV or history of HCV < 6 months prior to start of study treatment*)

12. In patients with a history of HBV, hepatitis B core antibody testing is required and if positive, then hepatitis B DNA testing will be performed and if positive the patient will be excluded.

13. Uncontrolled or severe cardiovascular disease, including myocardial infarction, unstable angina, or atrial fibrillation within 6 months prior to the start of study treatment; New York Heart Association Class II or greater congestive heart failure; serious arrhythmias requiring medication for treatment; clinically significant pericardial disease; cardiac amyloidosis; or QT interval corrected (QTc) with Fridericia's correction (QTcF) that is unmeasurable or ≥ 480 msec on Screening ECG. *NOTE: For QTcF ≥ 480 msec on the Screening ECG, the ECG may be repeated twice at least 24 hours apart; the mean QTcF from the 3 Screening ECGs must be < 480 msec in order to meet eligibility for trial participation.*

14. Gastrointestinal disease or disorder that could interfere with the swallowing, oral absorption, or tolerance of study treatment. This includes uncontrolled diarrhea (> 1 watery stool/day), major abdominal surgery, significant bowel obstruction, and/or gastrointestinal diseases that could alter the assessment of PK or safety, including but not limited to irritable bowel syndrome, ulcerative colitis, Crohn's disease, and hemorrhagic coloproctitis.

15. History of other invasive malignancy, unless adequately treated with curative intent and with no known active disease present within 2 years prior to the start of study treatment, provided it is deemed to be at low risk for recurrence by the treating physician
    NOTE: These latter conditions include but are not limited to non-melanoma skin cancer, carcinoma in situ [including superficial bladder cancer and cervical intraepithelial neoplasia], and organ-confined prostate cancer.

16. Concomitant use of drugs with a known risk of causing prolonged QTc and/or Torsades de Pointes or a history of risk factors for Torsades de Pointes (eg, familial long QT syndrome, heart failure, left ventricular hypertrophy). *See crediblemeds.org for a list of drugs that may prolong QT by risk category.*

17. Pregnant or lactating

18. Systemic fungal, bacterial, viral, or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

19. Any other severe, acute, or chronic medical, psychiatric, or social condition, or laboratory abnormality that may increase the risk of trial participation or study treatment administration,

may interfere with the informed consent process and/or with compliance with the requirements of the trial, or may interfere with the interpretation of the trial results and, in the Investigator's opinion, would make the patient inappropriate for entry into this trial.

20. B-cell NHL of the following subtypes:
    a. Burkitt lymphoma
    b. Lymphoblastic lymphoma or leukemia
    c. Post-transplantation lymphoproliferative disorder
    d. Known primary mediastinal, ocular, or epidural DLBCL

Exclusion Criteria for Part B – PCNSL Expansion Cohorts of Combination Therapy

1. Patients with only intraocular PCNSL without brain lesion or CSF involvement or T-cell lymphoma or systemic presence of lymphoma, or non-CNS lymphoma metastatic to the CNS
2. Prior history of malignancies other than lymphoma (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast) or prior history of systemic lymphoma, unless the patient has been free of the disease for ≥ 3 years.
3. Active malignancy other than PCNSL requiring systemic therapy
4. History of Grade ≥ 3 rhabdomyolysis without complete recovery
5. Patient has received external beam radiation therapy to the CNS within 28 days prior to Cycle 1 Day 1.
6. Prior investigational drugs (including treatment in clinical research, unapproved combination products, and new dosage forms) within 28 days or 5 half-lives, whichever is shorter, prior to Cycle 1 Day 1; allogeneic hematopoietic stem cell transplant (HSCT) within 60 days prior to C1D1; or clinically significant graft-versus-host disease (GVHD) requiring ongoing up-titration of immunosuppressive medications prior to Screening

   Note: The use of a stable or tapering dose of immunosuppressive therapy post-HSCT and/or topical steroids for ongoing skin GVHD is permitted with Sponsor Medical Monitor approval
7. Any prior systemic anti-cancer treatment such as chemotherapy, immunomodulatory drug therapy, etc., received within 21 days or 5 half-lives, whichever is shorter, prior to Cycle 1 Day 1 (with the exception of ibrutinib for Parts A2 and B, which may be continued as part of this study without interruption)
8. Receiving the following medications within 7 days prior to Cycle 1 Day 1:
   a. Medications which, in the opinion of the Investigator, have a high risk of causing prolonged QTc and/or Torsades de Pointes (Appendix L)
   b. Peg-filgrastim or equivalent
   c. St John's Wort
9. History of stroke or intracranial hemorrhage within 6 months prior to Cycle 1 Day 1. Patients with post-biopsy hemorrhagic sequela defined as a small hyperdense lesion < 3 mm on T2 sequence will not be excluded.
10. Patients who require anticoagulation with warfarin or equivalent vitamin K antagonists, including dual antiplatelet agents, within 5 half-lives of the anti-coagulant or 14 days,

whichever is longer, prior to Cycle 1 Day 1. Patients who require the use of antiplatelet agents should be discussed with the Sponsor Medical Monitor.

11. Vaccinated with live-attenuated vaccines within 4 weeks prior to Cycle 1 Day 1
12. Concomitant systemic corticosteroid on an ongoing basis within 14 days prior to Cycle 1 Day 1, with the exception of the following:
    a. Equivalent of up to 10 mg/day of prednisone for a disease other than PCNSL
    b. Equivalent of up to 50 mg/day of prednisone (equal to 8 mg/day of dexamethasone) for patients with lesions of the brain or spinal cord or both
13. Requires treatment with strong cytochrome P450 (CYP3A4) inhibitors or has received a strong CYP3A4 inducer or P-glycoprotein inducer within 7 days prior to Cycle 1 Day 1
14. Prior history of hypersensitivity or anaphylaxis to CA-4948 or ibrutinib or any excipients
15. Prior history of Stevens Johnson syndrome or toxic epidermal necrolysis
16. Patient who is intolerant of contrast-enhanced MRI due to allergic reactions to contrast agents
17. Major surgery, other than diagnostic surgery, < 28 days prior to Cycle 1 Day 1; minor surgery < 7 days prior to Cycle 1 Day 1

    Note: Insertion of a vascular access device is not considered minor surgery.
18. Viral infections:
    a. Known to be HIV positive or have an acquired immunodeficiency syndrome-related illness. If HIV is undetectable or maintained on treatment, enrollment may be allowed after discussion with the Sponsor
    b. HBV DNA positive or HCV infection < 6 months prior to Cycle 1 Day 1 unless viral load is undetectable, or HCV with cirrhosis

       Note: testing required only in patients with history of HBV or history of HCV <6 months prior to Cycle 1 Day 1.
    c. Active systemic infection, including a HIV, cytomegalovirus infection or SARS-CoV-2, or has had, within 28 days prior to Cycle 1 Day 1, an infection (other than nail trichophytosis) that requires hospitalization or an intravenous antibiotic
19. Concomitant illness that would preclude safe participation in study, including:
    a. Uncontrolled or severe cardiovascular disease, including myocardial infarction or unstable angina within 6 months prior to Cycle 1 Day 1, New York Heart Association Class II or greater congestive heart failure or left ventricular ejection fraction < 40% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan, serious arrhythmias uncontrolled on treatment, clinically significant pericardial disease, cardiac amyloidosis, or QTcF that is unmeasurable or > 450 msec on Screening electrocardiogram (ECG)

       Note: For QTcF > 450 msec on the Screening ECG, the ECG may be repeated twice at least 24 hours apart; the mean QTcF from the 3 Screening ECGs must be ≤ 450 msec in order to meet eligibility for trial participation. Patients with bundle branch block and/or ventricular paced rhythms should be reviewed by the Sponsor Medical Monitor for potential inclusion.

b. Gastrointestinal disease or disorder that could interfere with swallowing, oral absorption, or tolerance of study treatment. This includes major abdominal surgery and/or significant bowel resection and/or gastrointestinal diseases that could alter the assessment of PK or safety.
c. Known bleeding diathesis
d. Any other severe, acute, or chronic medical, psychiatric or social condition, or laboratory abnormality that may increase the risk of trial participation or study treatment administration, may interfere with the informed consent process and/or with compliance with the requirements of the trial, or may interfere with the interpretation of the trial results and, in the Investigator's opinion, would make the patient inappropriate for entry into this trial
e. Uncontrolled hypertension or electrolytic imbalance

20. Pregnant or lactating female

21. Patients with history of hemophagocytic lymphohistiocytosis (HLH)

CA-4948 Dose and Mode of Administration:

CA-4948 drug product is formulated as an immediate release film-coated tablet. Further details are available in the Pharmacy Manual.

During Part A1 (closed to enrollment), CA-4948 will be administered either QD or BID in continuous, consecutive 21-day treatment cycles. In order to provide greater trough exposure as indicated by current data, patients enrolled in Part A1 beginning with protocol v5.0 and all patients in Parts A2 (closed to enrollment) and B will receive CA-4948 BID. At all dose levels in Part A1 and at the 200 and 300 mg BID dose levels in Part A2, CA-4948 will be administered consecutively on every day of each 21-day cycle. In Part B, CA-4948 will be administered at 100 mg BID or 200 mg BID in combination with ibrutinib in a consecutive 28-day cycle.

Patients will take the dose of CA-4948 orally with water (no food 2 hours prior and 1 hour after) at approximately the same time each day. For BID dosing, doses should be administered at approximately the same time each day, approximately 12 hours apart.

Ibrutinib Dose and Mode of Administration:

Ibrutinib will be administered at a dose of 560 mg QD in continuous 21-day cycles for Part A2 and in continuous 28-day cycles for Part B. In Part A2, for WM/LPL and CLL/SLL, ibrutinib will be administered at a dose of 420 mg QD in continuous 21-day cycles. Ibrutinib should be administered QD at approximately the same time each day. The dose should be taken orally with a glass of water and may be administered at the same time as CA-4948.

Capsules should not be opened, broken, or chewed. Tablets should not be cut, crushed, or chewed. If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra doses of ibrutinib should not be taken to make up for the missed dose.

Duration of Treatment: For Part A, each treatment cycle will be 21 days in length. For Part B, the treatment cycle will be 28 days in length. Patients will be treated until intolerable toxicity progression of disease, or withdrawal or study termination.

Statistical Analysis:

Sample Size Considerations: The estimated sample size of up to approximately 60 patients in Part A is based on the standard 3 + 3 study design for dose escalation. The exact number of patients will be determined by the number of cohorts required to establish the MTD and RP2D for CA-4948 when administered as monotherapy and in combination with ibrutinib.