**NP39461**

**INCLUSION CRITERIA** Patients are eligible to be included in the study only if all of the following criteria apply:

**Informed Consent**

1. Able and willing to provide written informed consent and to comply with the study protocol according to ICH and local regulations.

**Age**

2. Age ≥ 18 years.

**Type of Patients and Disease Characteristics**

3. Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2.

4. Life expectancy > 3 months as per investigator’s assessment.

5. Patients with DLBCL relapsed or refractory to ≥ 1 course of chemotherapy including an anti-CD20 monoclonal antibody, and not eligible for ASCT (including due to chemorefractory disease). Patients with transformed FL are eligible, provided DLBCL histology is biopsy-confirmed prior to study entry and a treatment regimen as described above has been administered. The Sponsor retains the option to limit the number of participants enrolled with transformed FL.

6. Acceptable liver function, as specified below: • Total bilirubin ≤ 2 times upper limit of normal (ULN). (Patient with known Gilbert’s disease who has serum bilirubin ≤ 3 × ULN may be enrolled). • Aspartate transaminase (AST; SGOT), alanine transaminase (ALT; SGPT) ≤ 2.5 × ULN, (or ≤ 5 × ULN if tumor involvement (liver) is present). • Gamma-glutamyl transferase (GGT) alkaline phosphatase ≤ 2.5 × ULN.

7. Acceptable renal function, as specified below:: • Creatinine clearance (CrCl) calculated by Cockroft-Gault formula of ≥ 60 mL/min.

8. Acceptable hematologic status (growth factors cannot be used within the previous 7 days), as specified below: • Absolute neutrophil count (ANC) ≥ 1000 cells/μL • Hemoglobin ≥ 9 g/dL • Platelet count ≥ 75,000 (platelets/μL)

9. Serum calcium (corrected for albumin) level at or below the ULN (treatment of hypercalcemia is allowed and patient may enroll if hypercalcemia returns to normal with standard treatment). 10. Acceptable coagulation status, as specified below: • Prothrombin time (PT)/partial thromboplastin time (PTT) ≤ 1.2 × ULN (unless receiving anticoagulation therapy, if receiving anticoagulation therapy, eligibility will be based upon international normalized ratio [INR]). • INR ≤ 1.6 (unless receiving anticoagulation therapy). • If receiving warfarin: INR ≤ 3.0 and no active bleeding (i.e., no bleeding within 14 days prior to first dose of study therapy).

**Sex**

**11. Male and/or female participants** The contraception and abstinence requirements are intended to prevent exposure of an embryo to the study treatment. For all participants, the reliability of sexual abstinence must be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. a) **Male Participants** During the treatment period and for 4 months after the last dose of RO6870810/venetoclax or for 12 months after last dose of treatment of RO6870810/venetoclax co-administered with rituximab, agreement to: **–** Refrain from donating sperm; **–** Remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures such as a condom with partners who are women

of childbearing potential (as defined in Appendix 6) or pregnant female partners to avoid exposing the embryo.

b) **Female Participants**

• Women of non-childbearing potential, as defined in Appendix 6.

• Women of childbearing potential who:

**–** Agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for 2 months after the last dose of RO6870810/venetoclax or for 12 months after last dose of treatment of RO6870810/venetoclax co-administered with rituximab.

Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal occlusion, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices (see Appendix 6).

**–** Have a negative pregnancy test (blood) within the 7 days prior to the first study drug administration.

**5.2 EXCLUSION CRITERIA**

Patients are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Current central nervous system (CNS) lymphoma or leptomeningeal infiltration.

2. New York Heart Association (NYHA) Class III or IV cardiac disease, myocardial infarction, within the past 6 months, unstable arrhythmia, or known pericardial disease.

3. Fredericia-corrected QT interval (QTcF) > 470 msec (female) or > 450 msec (male), or history of congenital long QT syndrome.

4. Any electrocardiogram (ECG) abnormality, which in the opinion of the Investigator would preclude safe participation in the study.

5. Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy.

6. Known clinically important respiratory impairment (e.g., diagnosis of obstructive lung disease including patients with forced expiratory volume in the first 1 second of expiration [FEV1] < 60% of the predicted value, diagnosis of restrictive lung disease including patients with total lung capacity [TLC] < 60% of predicted value or history of idiopathic pulmonary fibrosis).

7. Grade ≥ 3 sensory or motor neuropathy.

8. Any Grade > 1 (according to the NCI CTCAE 4.03) adverse reaction unresolved from previous treatments and not readily managed and controlled with supportive care. The presence of alopecia (any grade) or Grade ≤ 2 peripheral neuropathy without pain is allowed.

9. Serious non-malignant disease that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.

10. History of PML.

11. History of other malignancy within 2 years prior to screening, except for ductal carcinoma in situ not requiring chemotherapy, appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, low-grade, localized prostate cancer (Gleason score ≤ 7) not requiring treatment or appropriately treated Stage I uterine cancer.

12. Completion of ASCT within 100 days prior to Day 1 of Cycle1.

13. Prior standard or investigational anti-cancer therapy, as specified below:

• Radio-immunoconjugate within 12 weeks prior to Day 1 of Cycle 1.

• Monoclonal antibody or antibody-drug conjugate (ADC) therapy within 3 weeks prior to Day 1 of Cycle 1.

• Radiotherapy, chemotherapy, or targeted small-molecule therapy within 2 weeks prior to Day 1 of Cycle 1.

14. History of major solid organ transplant (i.e., heart, lungs, liver and kidney).

15. History of an allogeneic bone marrow transplant.

16. Major surgical procedure within 28 days prior to Day 1 of Cycle 1.

**Prior/Concomitant Therapy**

17. Treatment with systemic corticosteroids ≥ 20 mg/day prednisone or equivalent, for non-lymphoma treatment reasons. For lower acceptable doses, documentation of a stable dose for at least 4 weeks prior to Day 1 of Cycle 1 is required. If corticosteroid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, up to 100 mg/day of prednisone or equivalent can be given for a maximum of 5 days. In such cases, all screening tumor assessments should be completed after completion of the steroid, but prior to start of first study treatment.

18. Treatment with strong to moderate CYP3A inhibitors or moderate CYP3A inducers within 7 days prior to the first dose of study treatment.

19. Treatment with strong CYP3A inducers within 14 days prior to the first dose of study treatment of RO6870810/venetoclax.

20. Consumption of grapefruits, grapefruit products, Seville oranges (including marmalade that contains Seville oranges), or star fruit within 3 days prior to the first dose of venetoclax.

**Prior/Concurrent Clinical Trial Experience**

21. Patients who are currently receiving any other investigational agent or have received an investigational agent within 30 days or 5 half-lives prior to study entry, whichever is longer.

22. Prior treatment with small molecule BET family inhibitor.

**Diagnostic Assessments**

23. Known to be human immunodeficiency virus (HIV) positive.

24. Presence of positive test results for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HcAb) (for patients receiving regimen including rituximab)

• Patients who are positive for HcAb must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participations

• Patients with occult or prior HBV infection (defined as positive total hepatitis B core antibody [HBcAb] and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.

**Other Exclusions**

25. Pregnant or breastfeeding female.

26. Significant allergy to a biological pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the participant.

27. Uncontrolled cancer pain. Participants requiring pain medication must be on a stable regimen at study entry. Symptomatic lesions amenable to palliative radiotherapy should be treated prior to enrollment.

28. History of severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies (for participants receiving regimen including rituximab).

29. Known sensitivity or allergy to murine products or any component of RO6870810, venetoclax, or rituxima