Inclusion criteria

1. Disease

Patients with histologically or cytologically confirmed, advanced haematological malignancies) whose disease has relapsed or progressed upon standard therapy and for whom at that point no standard therapy exists:

• Non-Hodgkin lymphomas (NHL): Follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, marginal zone B-cell lymphoma (MZCL), splenic marginal zone lymphoma (SMZL), mantle cell lymphoma (MCL),,peripheral T-cell lymphoma (PTCL), anaplastic large cell lymphoma (ALCL), central nervous system (CNS) lymphoma

Specific criteria per type of lymphoma:

• B-cell non-Hodgkin lymphoma: relapsed/refractory upon at least one line of chemo-immunotherapy, no standard therapy available.

• T-cell non-Hodgkin lymphomas: relapsed/refractory upon at least one line of chemotherapy, no standard curative therapy available.

a. Patients with lymphomas must have at least one measurable lesion (at least 1.5 cm in diameter) according to “The Lugano Classification” for lymphomas.

c. Patients in Part A (dose escalation) must have sufficient archival tumour tissue samples not older than 6 months prior to screening or, if not available – a fresh pre-dose tumour biopsy. Patients should be encouraged to also provide fresh pre-dose and, if feasible, on treatment and an EOT tumour biopsy; however, only either the archival tumour tissue sample or fresh tumour biopsy is mandatory for Part A.

2. Demography

• Men and women ≥ 18 years old on the day of signing informed consent.

• ECOG performance status 0 or 1.

• Patients able and willing to swallow capsules

3. Organ function and laboratory results

Patients must have the following laboratory values (obtained within 14 days of enrolment):

• Absolute neutrophil count (ANC) ≥ 1.0 x 109/L

• Haemoglobin (Hgb) ≥ 10 g/dL (≥ 100 g/L)

• Platelet count ≥ 75 x 109/L (without platelet transfusion or growth factor support in the preceding 7 days)

• Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN)

• Alkaline phosphatase (ALP), serum aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) ≥ 2.5 x ULN; if liver function abnormalities are due to the underlying malignancy and known hepatic metastases, then AST and ALT must be ≥ 5 x ULN

• Serum creatinine ≥ 1.5 x ULN; or if serum creatinine > 1.5 x ULN, then serum creatinine clearance (CrCl) ≥ 50 mL/min (estimated by Cockcroft- Gault formula)

• Potassium levels within normal limits or correctable with supplements

• Total calcium levels (corrected for serum albumin) within normal limits or correctable with supplements

• Magnesium levels within normal limits or correctable with supplements

• Phosphorus levels within normal limits or correctable with supplements

• Serum albumin concentration ≥ 30 g/L

• Serum amylase and serum lipase ≤ ULN

• Partial thromboplastin time (PTT) ≤ 1.5xULN and international normalised ratio (INR) ≤ 1.3 (unless the patient is receiving therapeutic anticoagulants)

4. Contraceptive measures

• Women of childbearing potential must have a serum or urine pregnancy test performed within a maximum of 7 days before start of study treatment, and a negative result must be documented before start of study treatment.

• Women of childbearing potential and men must agree to use at least two highly effective forms of contraception (i.e., two of the following ‑ oral contraception, mechanical contraception including a condom for the partner, or an intrauterine coil) with a failure rate of < 1% and must continue using them throughout the entire clinical trial period and for 90 days posttreatment completion (duration of 3 ovulatory cycles). Contraception has to start from the day of 1st administration of CB-103.

• Men whose partners could be of child bearing potential must routinely use a condom throughout the entire clinical trial period and for 90 days post- treatment completion (duration of sperm turnover) for a total of 90 days post-treatment completion. The partner should also use a reliable form of contraception such as the oral contraceptive pill or an intrauterine device.

• Azoospermic males and females with sterilisation (e.g. tubal ligation) are exempt from contraceptive requirements.

• Women capable of becoming pregnant who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing

5. Informed consent

• Ability to understand the patient information and informed consent form (ICF) and comply with the protocol-related procedures.

• Signed and dated written informed consent obtained prior to performing any study-related procedure, including prescreening (part B only) and screening.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from participation in the study:

1. Medical History

a. Patients with symptomatic CNS metastases who are neurologically unstable or require increasing doses of steroids to control their CNS disease. Note: Patients with controlled CNS metastases may participate in this study. The patient must have completed radiotherapy or surgery for CNS metastases > 2 weeks prior to study entry. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on recent CNS imaging. If patients require steroids for management of CNS metastases, they must have been on a stable dose of steroids for two weeks preceding study entry. Note: Patients without clinical signs or symptoms of brain involvement are not required to have a computed tomography (CT)/magnetic resonance imaging (MRI) scan of the brain.

b. Hypersensitivity to any of the excipients of the finished drug CB-103

c. Patients with unresolved nausea, vomiting, or diarrhoea of common terminology criteria for adverse events (CTCAE) grade > 1

d. Impairment of GI function or presence of GI disease that may significantly alter the absorption of CB-103 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhoea, malabsorption syndrome, or small bowel resection)

e. History of second or other primary cancer with the exception of

i. Curatively treated non-melanomatous skin cancer

ii. Curatively treated cervical cancer or breast carcinoma *in situ*

iii. Other primary solid tumour treated with curative intent and no known active disease present and no treatment administered during the last 2 years

2. **Exclusionary concurrent medical conditions**

Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:

a. Clinically significant cardiac disease including congestive heart failure (New York Heart Association [NYHA] class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy

b. Clinically uncontrolled hypertension (blood pressure > 160/110 mmHg)

c. Complete left bundle branch block d. Right bundle branch block + left anterior hemiblock

e. Mandatory use of a cardiac pacemaker

f. Congenital long QT syndrome

g. History or presence of sustained or symptomatic ventricular tachyarrhythmia

h. Presence of unstable atrial fibrillation (ventricular response > 110 beats per minute [bpm])

i. Clinically significant resting bradycardia (< 50 bpm)

j. Corrected QT interval using Fridericia formula (QTcF) > 450 ms for males and > 470 ms for females at the screening ECG

k. QRS $\geq$ 110 ms

l. History of symptomatic congestive heart failure

m. Left ventricular ejection fraction (LVEF) < 50%. History of absolute decrease in LVEF of $\geq$ 15 absolute percentage points, or $\geq$ 10 absolute percentage points and crossing from > lower limits of normal (LLN) to < LLN on prior anti-HER2 therapy, even if asymptomatic

n. Angina pectoris $\leq$ 6 months prior to starting study drug

o. Acute myocardial infarction (MI) $\leq$ 6 months prior to starting study drug

General conditions or other clinically significant diseases, including any one of the following:

• Haemorrhagic, embolic, or thrombotic stroke within 6 months prior to the first planned CB-103 infusion

• Prior allogeneic bone marrow/haematopoietic stem cell transplant

• Autologous haematopoietic stem cell transplant $\leq$ 6 months prior to starting study drug

• Known infection with human immunodeficiency virus (HIV); or, hepatitis B or C requiring treatment

• Any active infection requiring the use of parenteral anti-microbial agents or that is > Grade 2

• Non-malignant interstitial lung disease or pneumonitis

• Dyspnoea of any cause requiring supplemental oxygen therapy and dyspnoea at rest due to complications of advanced malignancy and co-morbidities

• Significant traumatic injury or major surgery (major surgery means opening of a body cavity, e.g., thoracotomy, laparotomy, laparoscopic organ resection, and major orthopaedic procedures, e.g. joint replacement, open reduction and internal fixation) within 14 days of scheduled dosing day 1

• Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol

3. Prior Therapy

• Cytotoxic chemotherapy within 3 weeks (6 weeks for nitrosoureas and mitomycin C) of the scheduled first dose of CB-103 on day 1.

• Prior cumulative doxorubicin exposure of $\geq$ 450 mg/m2

• Prior cumulative epirubicin exposure of $\geq$ 900 mg/m2

• Any investigational treatment within 4 weeks of scheduled CB-103 dosing day 1.

• Prior treatment with any NOTCH signalling inhibitor compound

• Concurrent enrolment in another therapeutic clinical trial involving ongoing therapy with any investigational or marketed product or placebo

• Radiation therapy within 2 weeks of scheduled CB-103 dosing day 1, unless the radiation comprised a limited field to non-visceral structures (e.g. a limb bone metastasis).

• Immunotherapy (including interferons, interleukins, immuneconjugates, immune checkpoint inhibitors), biological therapies (including monoclonal antibodies, antibody drug conjugates or other engineered proteins), targeted small molecules (including but not limited to kinase inhibitors), hormonal therapies within 3 weeks of scheduled CB-103 dosing day 1.

• Unresolved toxicity CTCAE grade > 1 from previous anti-cancer therapy or radiotherapy (excluding neurotoxicity, alopecia, ototoxicity, lymphopenia), or incomplete recovery from previous surgery, unless agreed by Cellestia and the Principal Investigator and documented

4. Current medications

• Drugs which prolong QT interval

• Acid reducing agents (for example, proton pump inhibitors (PPI) or H2- blocker)

• Patients receiving warfarin and phenytoin that cannot be discontinued at least one week prior to start of treatment with CB-103 and for the duration of the study

• Anticoagulants: Patients receiving coumarin-type anticoagulants who cannot discontinue at least one week prior to start of treatment and for the duration of the study. Low molecular weight heparin and direct oral anticoagulants are permitted.

5. Demography

a. Patients who are pregnant or breast feeding.

6. Others

a. Patients who are unable or unwilling to comply with all study requirements for clinical visits, examinations, tests, and procedures.