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TITLE OF STUDY:

A phase II study to evaluate safety and efficacy of CB-103 in combination with Venetoclax in adolescent and adult patients with relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL)

Title (Abbreviated): CB-103 + Venetoclax in Relapsed/Refractory T-ALL or T-LBL

Department: Department of Pediatrics Patient Care, Division of Pediatrics, & Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX

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1. OBJECTIVES

1.1. Primary Objectives:

1.1.1. To characterize the safety and tolerability of CB-103 in combination with Venetoclax in adolescent (12 to 18 years) and adult (19 to 60 years) patients with relapsed/refractory T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL).

1.1.2. To assess the efficacy of CB-103 in combination with venetoclax by the overall response rate (ORR), defined as complete remission (CR) plus CR with incomplete blood count recovery (CRi) [1] plus partial remission (PR) [2], in adolescent and adult patients with relapsed/refractory T-ALL/T-LBL.

1.2. Secondary Objectives:

1.2.1. To assess whether the ORR to CB-103 in combination with Venetoclax is dependent on pre-treatment expression of Notch and/or BCL2 pathway.

1.2.2. To determine the preliminary assessment of CB-103 in combination with Venetoclax by other efficacy parameters such as minimal residual disease (MRD), duration of response (DoR), overall survival (OS), and event-free survival (EFS) in adolescent and adult patients with relapsed/refractory T-ALL/T-LBL.

1.3. Exploratory Objectives:

1.3.1. To explore potential correlations of ORR to treatment and additional pharmacodynamic (PD) markers, i.e., other oncogenic pathway activations that may co-occur at the start of treatment.

1.3.2. To evaluate how many patients are able to transition to Hematopoietic Stem Cell Transplant (HSCT)**:**

1.3.2.1. Either in the patients achieving CR after the induction and reinduction cycles;
1.3.2.2. Or in the patients with PR or stable disease (SD) after the induction and reinduction.

2. BACKGROUND AND RATIONALE

2.1. T-ALL Background

Approximately 15% and 25% of newly diagnosed cases of acute lymphoblastic leukemia (ALL) in children and adults, respectively, are T-cell ALL (T-ALL) and are historically linked with a poor prognosis [1,2]. T-ALL is characterized by an older age of onset than B-ALL, male sex preponderance, and inferior outcome in comparison to B-ALL [1]. Even with the most advanced treatment, the 5-year disease-free survival (EFS) of children is only around 75%, with about 30% of children with T-ALL still failing to respond, relapsing, or dying from the disease [3]. Traditional treatment regimens for adult acute lymphoblastic leukemia, including allogeneic hematopoietic cell transplantation, result in overall survival of approximately 40% [4].

2.2. Notch pathway and Notch inhibitors in T-ALL

In T-ALL, the most frequent actionable mutation is Notch1 [5]. Notch pathway signaling is commonly activated by Notch1 and FBXW7 gene mutations in T-cell ALL, and these are the most commonly mutated genes in pediatric T-cell ALL [Board P D T IN. Childhood acute lymphoblastic leukemia treatment (PDQ®)[M]//PDQ Cancer Information Summaries. National Cancer Institute (US), 2019].[15,148] Notch1-activating gene mutations occur in approximately 50% to 60% of T-cell ALL cases, and FBXW7-inactivating gene mutations occur in approximately 15% of cases, with the result that approximately 60% of cases have Notch pathway activation by mutations in at least one of these genes [6]. In T-ALL Notch1 and the strictly associated γ-secretase inhibitors were tested in late-stage

disease, with some responses of short duration and considerable gut toxicity [7]. The best study reported one CR and an overall 32% response rate in 25 patients with relapsed disease [8].

2.3. CB-103

2.3.1. Preclinical studies

CB-103 is a first-in-class small molecule pan-Notch inhibitor with a novel mechanism of action directly targeting the Notch transcriptional activation complex by inhibition of the NICD-CSL interaction [9]. In contrast to the aforementioned inhibitors, pan-Notch inhibitor CB-103 is binding to the Notch-specific transcription complex in the cell nucleus and unfolds its effects at the transcription level of Notch target genes at the most downstream and central location. Thereby CB-103 can inhibit transcriptional activation of Notch-related target genes, regardless of the mechanism of activation, at the most downstream location in the cell nucleus.

Pharmacodynamic (PD) and direct effect of CB-103 treatment on tumor proliferation and growth was studied ex vivo in 10 primary T-ALL patient blood samples and based on one of the Notch positive T-ALL patient samples in vivo in a patient derived (PDx) xenograft model of human T-ALL in NSG mice. CB-103 was shown to be effective both against primary human T-ALL samples ex vivo and in patients' derived T-ALL xenografts in mice.

In a pre-clinical study the potential additive or synergistic activity of CB-103 in combination chemotherapy agents was investigated in patient samples harbouring GOF mutations in NOTCH1 receptor. The effect of drug on cell proliferation/ cell death was determined by MTS and best dose/combination were confirmed by flow cytometry using Annexin V+ 7AAD staining or an alternative method.

Combination drugs tested were:

a. Nelarabine
b. Cytarabine
c. Gemcitabine
d. HDAC6 inhibitor (ACY1215)
e. Dexamethasone
f. Vincristine

The data revealed that in NOTCH mutated (GOF) T-ALL patient samples, CB-103 exhibit synergy with Cytarabine, Gemcitabine, Nelarabine, HDAC6 inhibitor and Vincristine (**Table 1**). This synergy between CB-103 and different chemotherapeutic agents enhances cell death in NOTCH + T-ALL leukemic blasts.

More interestingly, a synergy between CB-103 and Cytarabine, Gemcitabine,and Nelarabine was observed also in one of the two patients with Notch wild-type T-ALL.

Table 1: Summary of drug combination effect on primary T-ALL samples**:**

T-ALL sample	NOTCH mutation	Additional mutations	Combination drug and combination index (CI value). CI < 1 synergy; = 1 additive, >1 antagonsitic effect					
			Cytar-abine	Nelarabine	Gemcitabine	HDAC6 inhibitor (ACY1215)	Vincristine	Dexamethasone
PDTALL39	**NOTCH1 GOF**	**P53**	**<1**	**<1**	**<1**	**<1**	**nd**	**Nd**
PDTALL19	**NOTCH1 GOF**	-	**< 1**	**<1**	**<1**	**<1**	**nd**	**>1**
PDTALL46	**NOTCH1 GOF**	**FBXW7 & P53**	**<1**	**<1**	**<1**	**<1**	**<1**	**nd**
PDTALL47	**NOTCH3 GOF**	**FBXw7 & P53**	**<1**	**<1**	**<1**	**<1**	**nd**	**nd**
PDTALL9	**Wildtype**	-	**>1**	**>1**	**>1**	**>1**	**nd**	**nd**
PDTALL13	**Wildtype**	-	**<1**	**<1**	**<1**	**Nd**	**nd**	**nd**

2.3.2. Clinical studies

The clinical study, CB103-C-101 (NCT03422679) was a first-in-human (FIH) trial, open-label phase I/IIA study designed to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of CB-103 administered orally in adult patients with either locally advanced or metastatic solid tumours or haematological malignancies characterised by pathogenic activations of the NOTCH signalling pathway.

In cohorts 1-8, CB-103 was given at increasing doses up to 500 mg (free base) once daily (QD). The dose of 500mg QD, given orally, was declared as provisional recommended phase 2 dose (RP2D). Starting with dose group 9, CB-103 was given twice daily (BID). In cohorts 9-12, increasing doses from 250 to 500 mg BID were explored. From dose group 10, an intermittent dosing schedule was introduced whereby CB-103 was administered twice daily on 5 days on treatment followed by two days off treatment break.

The dose of 2x 500mg in an intermittent schedule (five days on treatment, two days off) was declared a safe dose by the Cohort Review Committee (CRC). An MTD was not reached in the study. The 2x 500mg dose in an intermittent schedule (5 days on treatment, 2 days off) was declared as RP2D based on the saturation in exposure observed at this dose level and the high levels of NOTCH target gene downregulation, which would not biologically support further escalating the dose, as well as the signs of clinical efficacy observed. FDA suggests that for ≥ 12-year-old adolescent patients no weight-related clinically relevant effect on drug pharmacokinetics or safety are expected, ≥ 12-year-old adolescent patients enrolled in this trial may receive the same fixed daily dose as administered in adults (Clinical Growth Charts web page under National Center for Health Statistics at the Centers for Disease Control and Prevention website (https://www.cdc.gov/growthcharts/clinical_charts.htm).

Overall safety data (N=79) indicates that CB-103 is well tolerated with 61% of all reported adverse events (AEs) being mild (Grade 1) or 27% moderate (Grade 2) in severity, and 11% Grade ⩾3. Cumulatively, a total of 699 treatment emergent AEs has occurred in 76 patients since study initiation, of which 285 AEs (41%) in 60 patients were considered related to the study drug.

Most of treatment-related AEs resolved without requiring medications or discontinuation of CB-103 dosing, and without sequelae. Overall, there have been no sign of cardiotoxicity and no QTc prolongation reported. The most common study drug-related AEs (⩾10%) were

nausea (21.5%), dyschromatopsia (19.0%), anaemia (16.5%), blurred vision (15.2%), dyspepsia (12.7%), diarrhoea (12.7%), fatigue (11.4%), and vomiting (11.4%).

Three SAEs were considered related to study drug (two drug-induced liver injury in two patients with progressive liver metastasis and Stevens-Johnson syndrome was diagnosed in a patient after she took amoxicillin/clavulanic acid). There were two DLTs. One patient in cohort 8 (500mg) experienced one dose limiting toxicity (DLT). This was an elevation of the gamma-glutamyl transferase (GGT), grade 3, that was asymptomatic and deemed not clinically significant by the investigator. One patient in cohort 11 (400mg BID) experienced visual impairment that led to treatment interruption which counts as DLT. After the patient switched to a once daily schedule, he continued treatment. No deaths due to drug-related AEs have been reported.

Individual patients have been treated with CB-103 under compassionate use in combination with other drugs (anticancer drugs and drugs for the prevention of GVHD). The combination treatment did not alter the safety profile of CB-103 and did not increase or worsen toxicities associated with the combination drugs. There were further signs of efficacy, particularly two patients with r/r T-ALL that achieved complete response.

In addition to demonstrating a favorable safety profile of CB-103, pharmacodynamic data have shown strong target engagement, down-regulation of key target genes as well as long-term stable disease in patients with Notch-pathway activation in Adenoid Cystic Carcinoma (ACC) [10]. Taking together the fact that Notch activation is an important driver of multi-drug resistance [10], the confirmed effect on the target, and exceptional safety profile in cancer patients, CB-103 is an ideal drug to be used in combination with standard of care therapies to tackle multi-drug resistant cancer.

2.4. Mitochondrial cell death pathway

The apoptotic blocking provided by BCL-2 expression has been shown to have a central role in survival of leukemic cells [11]. The mitochondrial cell death pathway is initiated by proapoptotic BH3-only effector proteins, which activate the cell death proteins including BAX and BAK [12]. The survival of cells depends on antiapoptotic family proteins (BCL- 2, BCL-X, and MCL1) that bind and sequester BH3-only effector protein, which in turn blocks activation of the cell death pathway.

Using BH3 profiling, a mitochondrial assay that classifies blocks in the intrinsic apoptotic pathway, Moore et al. [13] provided evidence that cells in the ALL samples exhibit dependence on BCL-2 by demonstrating inhibition of BCL-2 and killing of leukemic cells using a proapoptotic pharmacologic inhibitor of Bcl-2/Bcl-xL, ABT-737.

2.5. Venetoclax (ABT-199)

Venetoclax (ABT-199) is a novel, orally bioavailable small-molecule inhibitor of B-cell lymphoma 2 (BCL2), a key regulator of the intrinsic apoptotic pathway. Venetoclax has shown promising effects in hematologic malignancies including chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) [14, 15, 16]. Recent preclinical studies have suggested that inhibition of BCL-2 may be a novel therapeutic strategy for patients with T-ALL [17].

Two clinical trials will study the efficacy of venetoclax in monotherapy in RR ALL. A phase I study is recruiting pediatric patients and young adults with RR ALL to address the safety and pharmacokinetics of venetoclax monotherapy (NCT03236857). Another phase 1 study with dose escalation is underway and recruiting participants and will analyze the safety and pharmacokinetics of venetoclax, navitoclax, and chemotherapy in recurrent ALL (NCT03181126).

2.6. Rationale of the CB-103 + Venetoclax (ABT-199) combination

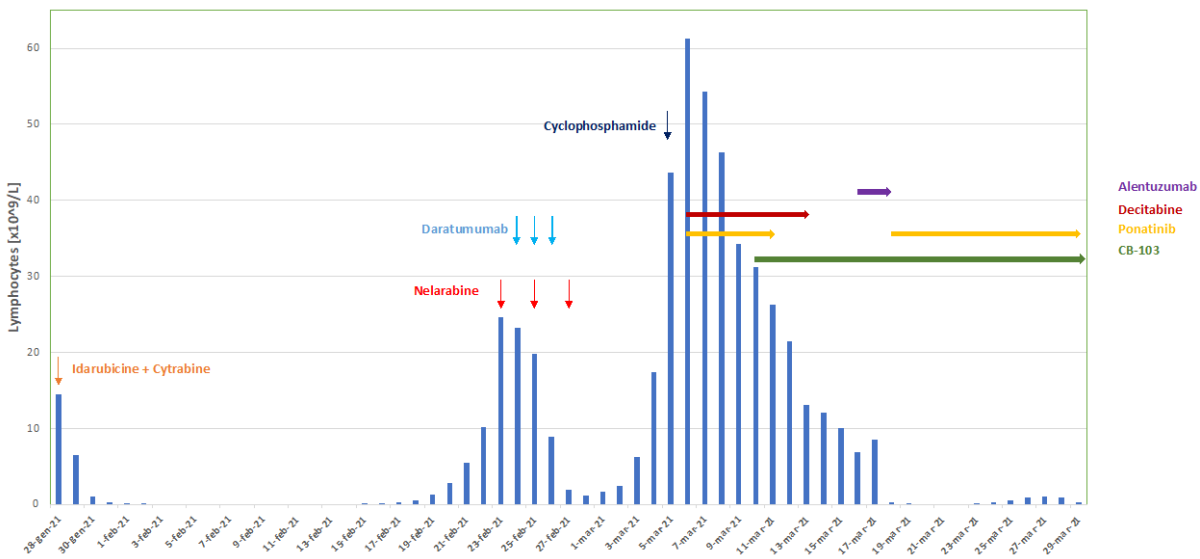
The combination of a γ-secretase inhibitor and a BCL2 inhibitor showed synergistic antitumor effects in multiple myeloma, breast cancer, melanoma and non-small cell lung cancer cell lines [18, 19, 20,21, 20]. This effect was mediated through a dramatic upregulation of the proapoptotic bcl-2 family protein Noxa [22].

Noxa belongs to the BH3-only "sensitizer" protein family that act by displacing the BH3-only "activators" like Bid and Bim from the antiapoptotic proteins, allowing the activators to bind Bax and Bak [23]. Alternatively, antiapoptotic proteins could directly inhibit Bax and Bak activation [24]. It is well known that Noxa has a very high affinity for the antiapoptotic protein Mcl-1, but not Bcl-2, Bcl-xL, or Bcl-w. While activation of Bax is controlled by Bcl-2, Mcl-1, and Bcl-xL, Mcl-1 also cooperates with Bcl- xL to sequester Bak and prevent its activation [25, 26]. Recent studies have indicated that targeting of both Mcl-1 and Bcl-xL is necessary in order to release Bak [27].

In both human primary T-ALL patient cell samples and in mouse xenograft transplants of adenoid cystic carcinoma, CB-103 + BCL2 inhibitor combination showed potent synergistic effect versus either single agent (data on file, Cellestia AG).

There is anecdotal evidence of the activity in human T-ALL of CB-103 combined with other targeted therapy from the compassionate use treatment of a 24-year old male patient (Data on file, Cellestia Biotech AG). The patient was diagnosed with T-ALL expressing a Notch1 mutation in 29% of blasts in May 2020: after achieving CR with the polychemotherapy GRAALL-2014 regimen in July 2020, the patient relapsed within a few months and became refractory to a series of salvage therapies, including idarubicine, cytarabine, neralabine, daraturumab, and cyclophosphamide. When all standard treatments were exhausted, a sequential/combined therapy with agents specifically targeted to the genetic alterations most frequently detected in the leukemic cells (BCL2, ABL1, CD-28 and Notch1) was adopted as the last attempt to transition the patient to HSCT (**Figure 1**): the patient was again induced into remission and was successfully transplanted.

Figure 1: Sequence of the combined agents and results on the circulating lymphocytes



The number of circulating lymphocytes is plotted versus days from the initial retreatment for relapsing disease: the sequential use and timing of of the variously single or combined agents is shown as well. Vertical arrows represent daily administration of the corresponding durg during the second attempt

to induce a remission, while orizontal arrows indicate the duration of administration of the corresponding durg during the third attempt to induce a remission.

The sequence of these events points out to:

- the validity of a targeted therapeutical approach on the basis of the phenotypic/genetic biomarkers of the disease;
- the possible contribution of a Notch inhibitor in at least abating the Notch1 mutated clone, that was present since the initial diagnosis;
- the possibility of adding a Notch inhibitor to more than one other targeted agents without additional safety concerns and a potential additive efficacy.

3. STUDY POPULATION

3.1. Inclusion Criteria:

3.1.1. Adolescent (12 to 18 years) and adult (19 to 60 years) patients who have relapsed or refractory T-cell lymphoblastic leukemia (T-ALL) or T-Cell lymphoblastic lymphoma (T-LBL) according to 2017 WHO classification [29] and NCCN v1 2021 [30]:

Patients must have ≥ 5% blasts in the bone marrow as assessed by morphology on standard bone marrow biopsy and aspirate or less than 5% blasts in the bone marrow in presence of extramedullary relapse, excluding isolated central nervous system (CNS) relapse. However, if an adequate bone marrow sample cannot be obtained, patients may be enrolled if there is unequivocal evidence of leukemia with ≥ 5% blasts in the peripheral blood.

3.1.2. Patients are eligible independently of Notch pathway activation in the leukemic blasts: however, a fresh marrow/blood sample must be obtained before starting the study treatment to classify the patients as being either Notch positive or negative.

3.1.3. Leukemic blasts must express of at least 2 of the following immune phenotyping: CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD34, TCRαβ, TCRγδ, cyCD3

3.1.4. Patients have adequate performance status (ECOG ≤2) for patients ≥16 years old, Lansky score >50 for patients <16 years old.

3.1.5. Patients must be 12 to 60 years of age inclusive when signing the informed consent. For patients < 18 years of age, parent or legally authorized representative (LAR) should be willing and able to give informed consent. Non-English speaking patients are eligible for whom consent process will follow institutional guidelines.

3.1.6. Patients with CNS disease are eligible.

3.1.7. Patients must have adequate organ function and laboratory results (obtained within 14 days of enrollment):

3.1.7.1. Direct bilirubin ≤2 x upper limit of normal (ULN).

3.1.7.2. 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).

3.1.7.3. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤3 x ULN; ≤5 x ULN in case of suspected leukemic liver involvement

3.1.8. Females of childbearing potential must have a negative serum or urine beta-human chorionic gonadotropin (β-HCG) pregnancy test result within 14 days prior to the first dose of study drugs and must agree to use one of the following effective contraception methods during the study and for 30 days following the last dose of study drug. Effective methods of birth control include:

3.1.8.1. Birth control pills, skin patches, shots, subdermal implants

3.1.8.2. Intrauterine devices (IUDs)

3.1.8.3. Condom or occlusive cap (diaphragm or cervical/vault caps) used with Spermicide

3.1.8.4. Abstinence

3.1.9. Males agree to inform study doctor right away if their partner becomes pregnant or suspects pregnancy. While in this study and for 30 days after the last treatment the patient agrees not to donate sperm for the purposes of reproduction. He agrees to use a condom while in this study and for 30 days after the last treatment**.**

3.2. Exclusion Criteria

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

3.2.1. Mixed phenotype leukemia (excluding T-ALL with myeloid antigen expression)

3.2.2. History of another primary invasive malignancy that has not been definitively treated and in remission. Patients with non-melanoma skin cancers or with carcinomas in situ are eligible regardless of the time from diagnosis (including concomitant diagnoses).

3.2.3. Presence of clinically significant uncontrolled CNS pathology such as epilepsy, childhood seizure, paresis, aphasia, stroke, severe brain injuries, organic brain syndrome, or psychosis.

3.2.4. Patients with a cardiac ejection fraction (as measured by either MUGA or echocardiogram) < 50% or with a history of absolute decrease in LVEF of ≥ 15 absolute percentage points are excluded.

3.2.5. Medical history of cardiovascular disease such as:

3.2.5.1. Clinically significant cardiac disease including congestive heart failure (NYHA class III or IV), arrhythmia or conduction abnormality requiring medication, or cardiomyopathy

3.2.5.2. Clinically uncontrolled hypertension

Age	Blood Pressure
12 to 13	>120/80mmHg
>13	>140/90mmHg

3.2.5.3. Complete left bundle branch block

3.2.5.4. Right bundle branch block + left anterior hemiblock

3.2.5.5. Congenital long QT syndrome

3.2.5.6. History or presence of sustained or symptomatic ventricular tachyarrhythmia, atrial fibrillation, or clinically significant resting bradycardia (< 50 bpm)

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

3.2.5.8. QRS ≥ 110 ms

3.2.5.9. History of symptomatic congestive heart failure

3.2.6. Patients with uncontrolled, active infections (viral, bacterial, or fungal). Infections controlled on concurrent anti-microbial agents are acceptable. Anti-microbial prophylaxis per institutional guidelines is acceptable.

3.2.7. Known active hepatitis B or C infection or known seropositivity for HIV.

3.2.8. Liver cirrhosis or other active severe liver disease or suspected active alcohol abuse.

3.2.9. Have conditions requiring chronic systemic (not inhaled) glucocorticoid use, such as autoimmune disease or severe asthma. Low doses of corticosteroids (10 mg prednisone equivalent a day) are permitted.

3.2.10. Patients with unresolved nausea, vomiting, or diarrhea of CTCAE version 5.0, grade > 1 from prior therapy.

3.2.11. Patients with impairment of GI function or GI disease presence that may significantly alter the absorption of CB-103 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

3.2.12. Have current or recurrent (within 3 months) gastrointestinal disease, have conditions requiring chronic systemic glucocorticoid use, have active graft versus host disease, or have a second primary or prior malignancy that would affect the interpretation of study results. Low doses of corticosteroids (10 mg prednisone equivalent a day) are permitted.

3.2.13. Prior chemotherapy/radiotherapy/investigational therapy within 2 weeks before the start of study drugs with the following exceptions:

3.2.13.1. Up to 5 days of glucocorticoids (10 mg of dexamethasone or equivalent/day) in combination with up to 3 doses of cyclophosphamide (200 mg/m^2/day) are allowed as standard pre-phase treatment up to 1 day before start of study treatment. Cytarabine up to 2gm/m2 are also allowed as standard pre-phase treatment up to 1 day before start of study treatment.

3.2.13.2. Mercaptopurine may be dosed up to 5 days prior to first dose of CB103

3.2.13.3. Vinca alkaloids may be dosed up to 5 days prior to first dose of CB103

3.2.13.4. Prophylactic intrathecal (IT) chemotherapy may be dosed up to 1 day prior to first dose of CB103

3.2.14. Females who are pregnant or lactating.

3.2.15. Male or female subjects of childbearing potential, unwilling to use an approved, effective means of contraception in accordance with institution's standards.

3.2.16. Other severe, uncontrolled acute or chronic medical or psychiatric condition or laboratory abnormality that in the opinion of the Investigator may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.

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

3.2.18. Patients must be excluded if they are currently enrolled in another ongoing clinical trial with anti-cancer investigational products

4. TREATMENT PLAN

4.1. Study Design

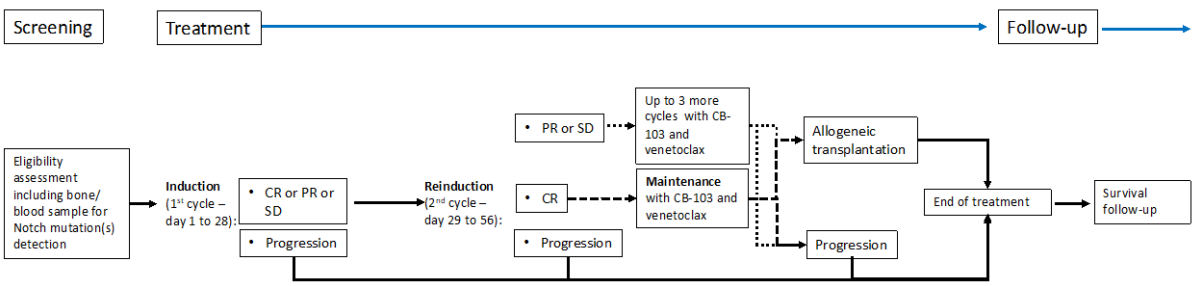
This study is designed as a phase II open-label single-arm clinical trial to evaluate the efficacy and safety of CB-103 in combination with venetoclax in adolescent and adult patients with T-ALL/T-LBL with relapsed or refractory disease.

Patients are eligible independently of Notch pathway activation in the leukemic blasts: however, a fresh marrow/blood sample must be obtained before starting the study treatment to classify the patients as being either Notch positive or negative. Notch pathway activation is defined presence of Notch1 gain-of-function (GOF) mutations, or FBXW7 loss-of-function (LOF) mutations, or Notch3 GOF mutations or Notch1 translocations detected by Next Generation Sequencing (NGS). Details on molecular alterations as signs of Notch pathway activation and the specific test method can be found in the laboratory manual.

The study consists of three periods (**Figure 2**):

- Screening period (including baseline assessments)
- Treatment period (including an End-of-Treatment [EOT] visit)
- Survival follow-up period

Figure 2: Study design schema



A cycle of treatment is defined as 28 days of treatment with CB-103 and Venetoclax.

4.2. Treatment Plan

4.2.1. Induction cycle

All eligible patients will receive the 1st cycle (**induction cycle**; day 1-28) with CB-103 and venetoclax.

4.2.2. Reinduction cycle

Patients achieving benefits from the treatment – benefit is defined as achieving at least stabilization of the disease - are eligible to receive a 2nd cycle (**reinduction cycle**, day 29-56) of CB-103 and venetoclax at the same dose as in the induction cycle.

In patients who did not attain a defined clinical response after the induction cycle i.e. non responders, a reinduction cycle of CB-103 and Venetoclax may be administered if there was no unacceptable toxicity.

4.2.3. Maintenance

Patients in CR or CRi after the reinduction cycle may continue to receive the combination CB-103 and venetoclax until disease progression or bone marrow transplantation.

Patients with PR or stable disease (SD) after the reinduction cycle may continue the treatment with the combination of CB-103 and venetoclax for a maximum of three additional cycles or until disease progression or bone marrow transplantation, whichevercomes first.

4.3. Duration of Treatment and End of Study

Patients will be followed-up for survival up to 2 years after they are enrolled onto the study.

Estimated Study period: Q4 2022 – Q4 2025

Collection of data will cease at the time when the last patient is removed from the study.

Patients that are removed from the study during cycle 1 for any reason other than toxicity or disease progression will be replaced.

Dose modifications/reductions are allowed in case of expected or observed unacceptable toxicity, at the discretion of treating physician or principal investigators.

4.3.1. End of 1st Cycle (induction cycle)

Patients are assessed for disease response on day 28 from the start of treatment (end of the **induction cycle**).

If the day 28 marrow is not hypocellular (cellularity $\leqslant$ 15%) and the patient is showing at least stabilization of the disease or a clinical benefit in the investigator's judgement, the patient may enter the **reinduction** cycle of CB-103 and venetoclax. Patients are defined to have a clinical benefit, if they are in complete remission (CR) or complete remission with incomplete blood count recovery (Cri), or have a decrease in disease burden, including peripheral blasts or bone marrow blasts that do not meet the criteria for CR or Cri, or have no evidence of progression.

If the day 28 marrow is hypocellular (cellularity $\leqslant$ 15%), then a repeat bone marrow biopsy is obtained between days 36 and 42 to assess response; if the repeat marrow is not hypocellular (cellularity $\leqslant$ 15%) and the patient is showing at least stabilization of the disease, the patient may enter the **reinduction** cycle of CB-103 and venetoclax.

If the peripheral counts do not recover (ANC < 1 x 10^9/L or platelets count < 60 x 10^9/L) and there is evidence of residual leukemia in the bone marrow, the patient may enter the **reinduction** cycle of CB-103 and venetoclax at the discretion of the treating physician, after a minimum of 4 weeks from the start of the last cycle.

Patients who do not attain a defined clinical response after the **induction** cycle, may enter the **reinduction** cycle of CB-103 and venetoclax if there was no unacceptable toxicity.

4.3.2. End of 2nd Cycle (reinduction cycle)

Patients are assessed for disease response on day 56 from the start of treatment (end of the **reinduction cycle**):

1. If the day 56 marrow is not hypocellular (cellularity ≤ 15%) and the patient is showing a CR or a CRi, the patient is eligible for **maintenance** with CB-103 and venetoclax until disease progression or bone marrow transplant in the absence of discontinuation criteria.
2. If the day 56 marrow is hypocellular (cellularity ≤ 15%), then a repeat bone marrow biopsy is obtained between days 66 and 70 to assess response; if the repeat marrow is not hypocellular (cellularity ≤ 15%) and the patient is showing a CR or a CRi, the patient is eligible for maintenance with CB-103 and venetoclax until disease progression or bone marrow transplant in the absence of discontinuation criteria.
3. Patients with PR or stable disease (SD) after the reinduction cycle may continue the treatment with the combination of CB-103 and venetoclax for a maximum of three additional cycles or until disease progression or bone marrow transplantation, whicher comes first.
4. Non-responding patients, i.e patients without Cr or Cri or PR or SD after the reinduction cycle are discontinued from the treatment.

4.3.3. End of Treatment

Treatment will continue until discontinuation due to unacceptable toxicity, lack of response, relapse or progressive disease. This includes any of the following:

1. Clinically significant progressive disease at any time.
2. Death
3. Possibility of undergoing allogeneic stem cell transplantation.
4. Intercurrent illness that prevents further administration of treatment.
5. Unacceptable adverse event(s), that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the Investigator, pose an unacceptable risk for the patient.
6. Patient decision for study withdrawal.

General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the Investigator, sponsor, or any regulatory body.

End of Treatment (EoT) visit is to be done 5 days after the last dose of any study treatment, unless the patient starts any subsequent antitumor therapy (in which case the EoT visit should be performed before the start of the new therapy, whenever possible).

4.3.4. Survival Follow-up

Patients will be followed-up for survival data up to 2 years after their study enrollment: survival status and any new anti-cancer therapy may be collected by phone every 3 months.

5. TREATMENTS ADMINISTERED

5.1. CB-103. CB-103 is a novel First-in-Class pan-Notch Protein-Protein Interaction (PPI) inhibitor directly targeting the assembly of the Notch transcription complex located in the nucleus of tumor cells. Thereby it inhibits transcription of Notch-related target genes at the most downstream location in the cell nucleus.

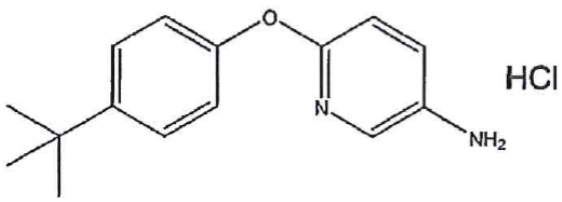
The Investigational Medicinal Product (IMP) CB-103 will be provided in the form of capsules for oral treatment.

More detailed information on the oral formulation of CB-103 can be found in the Investigator's Brochure.

5.1.1. Description. CB-103 is produced under good manufacturing practice (GMP) conditions and analysed using state-of-the-art methods to ensure identity, purity and safety. CB-103 HCl is a white to off-white powder, soluble in water, with discrete polymorphism and a melting point around 173°C. Aqueous solubility is pH-dependent with higher values at lower pH. The active pharmaceutical substance is 6-(4-(tert-butyl) phenoxy) pyridin-3-amine hydrochloride with a molecular weight of 278.78 g/mol (hydrochloride) and 242.32 g/mol (free base). CB-103 is provided to patients as capsules or oral suspension for oral administration.

5.1.2. Nomenclature, structure and molecular weight.
Chemical name: 6-(4-(tert-butyl)phenoxy)pyridin-3-amine hydrochloride Laboratory code: CB-103.

Figure 3: Structure of CB-103 HCl



Molecular Formula: C15H18N2O · HCl (hydrochloride);
Molecular weight: 278,78 g/mol (CB-103 hydrochloride); 242.32 g/mol (CB-103 free base).

5.1.3. Dosage and Administration.
CB-103 will be administered orally as 500 mg twice a day (BID) for 5 days on and 2 days off, which has now been declared the RP2D in adults (**section 2.3.2 Clinical Studies**), until disease progression per investigator's judgement, or until unmanageable drug related toxicity, or as long as the patients are continuing to derive clinical benefits (**section 4.2 Treatment Plan**). For patients already enrolled prior to Protocol Version 2.0, they will be reconsented and offered the increased dose if it is felt to be safe and in the patient's best interest by the treating physician, otherwise they may continue at their current dose of 500 mg daily.

In the event of vomiting, no re-dosing will be provided. According to FDA recommendations, as for ≥ 12-year-old adolescent patients no weight-related clinically relevant effect on drug pharmacokinetics or safety are expected, ≥ 12-year-old adolescent patients enrolled in this trial may receive the same fixed daily dose as administered in adults (Clinical Growth Charts web page under National Center for Health Statistics at the Centers for Disease Control and Prevention website (https://www.cdc.gov/growthcharts/clinical_charts.htm).

CB-103 will be provided as capsules of 100 mg each. Patients will be instructed to swallow the CB-103 capsules whole with a glass of water (approx. 200 mL) in the morning, on an empty stomach, at least one hour before taking breakfast; in the evening, within 8 to 12 hours of the first intake, at least one hour before the evening meal. Capsules should not be chewed prior to swallowing. Capsules that are broken, cracked, or otherwise damaged should not be ingested. In the exceptional case of a patient who is unable to swallow capsules, the capsules can be opened and the contents may be mixed in a spoon with a bit of yogurt or fruit puree in order to swallow and follow with a glass of approximately 200mL of water (IMP Manual).

5.1.4. Drug Preparation, Storage and Handling. All drug supplies should be stored in a secure, temperature-controlled area, which can be accessed only by the pharmacist, the Investigator, or another duly designated person. The investigational site will be supplied with study drug according to the site's needs. Patients should be given a sufficient supply to last until their next study visit. Detailed storage conditions will be provided on the medication label and on the Pharmacy Manual. Detail drug preparation instructions are provided in the manufacturer's full prescribing information brochure. Unused portions of the study drug will be discarded properly as per the institutional policies.

5.1.5. Drug Accountability. To ensure adequate records, CB-103 capsules will be accounted for as follows:

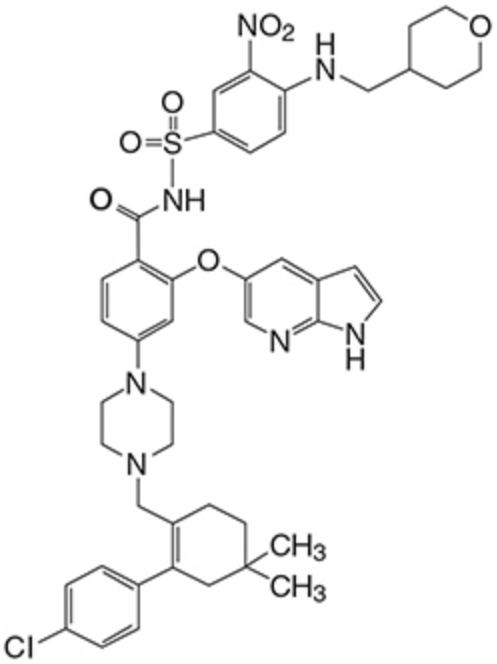
- patients have a diary where they document the number of capsules taken each day;
- patients are requested to return previously dispensed packages with the unused study drug as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be dispensed with new medication at that visit;
- the Investigator or designee will review the patient diary at Day 1 of each cycle.

5.2. Venetoclax. Venetoclax is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy.

Venetoclax is a selective and orally bioavailable small-molecule inhibitor of BCL-2, an antiapoptotic protein. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein, displacing proapoptotic proteins like BIM, triggering mitochondrial outer membrane permeabilization and the activation of caspases. In nonclinical studies, venetoclax has demonstrated cytotoxic activity in tumor cells that overexpress BCL-2.

5.2.1. Description.
Venetoclax is a selective inhibitor of BCL-2 protein. It is a light yellow to dark yellow solid with the empirical formula C45H50ClN7O7S and a molecular weight of 868.44. Venetoclax has very low aqueous solubility. Venetoclax is described chemically as 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-N-({3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide) and has the following chemical structure:

Figure 4: Structure of Venetoclax: a selective and orally bioavailable small-molecule inhibitor of BCL-2.



Venetoclax tablets for oral administration are supplied as pale yellow or beige tablets that contain 10, 50, or 100 mg venetoclax as the active ingredient. Each tablet also contains the following inactive ingredients: copovidone, colloidal silicon dioxide, polysorbate 80, sodium stearyl fumarate, and calcium phosphate dibasic. In addition, the 10 mg and 100 mg coated tablets include the following: iron oxide yellow, polyvinyl alcohol, polyethylene glycol, talc, and titanium dioxide. The 50 mg coated tablets also include the following: iron oxide yellow, iron oxide red, iron oxide black, polyvinyl alcohol, talc, polyethylene glycol and titanium dioxide.

5.2.2. Dosage and Administration.

Venetoclax is an oral medication that is taken continuously once daily with food and water: patients should take tablets with a meal and water at approximately the same time each day. Tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. Tablet may be split in half to allow for more accurate dosing. It will be administered according to the following dose schedule (**Table 2**). Compliance will be verified by counting the tablets provided per day during clinic visits.

Table 2: Venetoclax ramp-up dose schedule

Dosing	Day 1	Day 2	Day 3 and onward
Adolescent or adult patients	100 mg/day	200 mg/day	400 mg/day

Tables 3 and 4 provide recommendations for management and potential interactions with CYP3A and P-gp inhibitors and examples of drugs that interact with venetoclax.

Concomitant use of venetoclax with *strong* CYP3A inhibitors and inducers at initiation and during the ramp-up phase is not recommended due to the potential for increased risk of tumor lysis syndrome (TLS). If use of a strong CYP3A inhibitor is deemed necessary, Venetoclax dose should be modified according to **Table 3**. Concomitant use of venetoclax with strong or moderate CYP3A inducers is not recommended throughout the study period. Concomitant strong or moderate CYP3A or P-gp inhibitors must have reached steady state prior to venetoclax initiation and must also not be discontinued until after the initiation and ramp-up phase of venetoclax. If a concomitant strong or moderate CYP3A inhibitor or P-gp inhibitor is discontinued after the initiation and ramp-up phase, increase venetoclax to 400 mg/day 2 to 3 days after discontinuation of the inhibitor. Reduce venetoclax once-daily dose by 50% for patients with severe hepatic impairment (Child-Pugh C); monitor these patients more closely for signs of toxicity.

Table 3: Management of potential venetoclax interactions with CYP3A and P-gp inhibitors*****

Coadministered drug	**Initiation and ramp-up phase**	**Steady daily dose(after ramp-up phase)**
Posaconazole	Start at 10 mg on day 1, followed by 20 mg on day 2, 50 mg on day 3, and 70 mg on day 4	Reduce the venetoclax dose to 70 mg
Other strong CYP3A inhibitor	Start at 10 mg on day 1, followed by 20 mg on day 2, 50 mg on day 3, and 100 mg on day 4	Reduce the venetoclax dose to 100 mg
Moderate CYP3A inhibitor	Reduce the venetoclax dose by at least 50%	
P-gp inhibitor		

*****Consider alternative medications or reduce the venetoclax dose as described in this table. CYP3A=cytochrome P450; P-gp=P-glycoprotein.

Table 4 : Examples of CYP3A and P-gp inhibitors/inducers*

Coadministered drug	**Name**
Other strong CYP3A inhibitor	Clarithromycin, Conivaptan, Diltiazem, Indinavir, Itraconazole, Ketoconazole, Lopinavir, Ritonavir, Telaprevir, Voriconazole, Posaconazole
Moderate CYP3A inhibitor	Aprepitant, Cimetidine, Ciprofloxacin, Cyclosporine, Dronedarone, Erythromycin, Fluconazole, Isavuconazole, Verapamil
P-gp inhibitor	Amiodarone, Carvedilol, Clarithromycin, Cyclosporine, Dronedarone, Itraconazole, Ketoconazole, Quinidine, Ranolazine, Ritonavir, Verapamil, Posaconazole
Strong CYP3A inducer	Carbamazepine, Phenytoin, Rifampin, St. John's wort
Moderate CYP3A inducer	Bosentan, Efavirenz, Etravirine, Modafinil

*This is not an exhaustive list and is intended only to complement, not replace, clinical judgment during treatment of patients with venetoclax. Please refer to the FDA website for more examples.

5.2.3. Risk Assessment and Prophylaxis for Tumor Lysis Syndrome (TLS)

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Perform tumor burden assessments, including radiographic evaluation (e.g., CT scan), assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) in all patients and correct pre-existing abnormalities prior to initiation of treatment with venetoclax. Reduced renal function (creatinine clearance [CrCl] <80 mL/min) further increases the risk.

Patients with ALL at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested initial studies, obtained prior to initiating antileukemia therapy, may include a complete blood count (CBC), prothrombin (PT) and activated partial thromboplastin times (aPTT)and serum electrolytes, including creatinine, BUN, uric acid, phosphorus, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

Recommended TLS prophylaxis based on Tumor Burden from clinical trial data (consider all patient co-morbidities before final determination of prophylaxis and monitoring schedule) is shown in **Table 5**:

Table 5: TLS Prophylaxis

Tumor Burden		**Prophylaxis**	
		Hydration	**Anti-hyperuricemics**
Low	Any LN <5cm AND ALC <25 x10^9/L	Oral (1.5-2 L)	Allopurinol
Medium	All LN >5cm to <10cm AND ALC ≥25 x10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol
High	Any LN ≥10cm OR ALC ≥25 x10^9/L AND any LN ≥5cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol: consider rasburicase if baseline uric acid is elevated
ALC = absolute lymphocyte count; LN = lymph node. Administer intravenous hydration for any patient who cannot tolerate oral hydration. Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax. Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time. For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and 24 hours at each subsequent ramp-up dose.			

5.2.4. Drug Preparation, Storage and Handling. Detail drug preparation instructions are provided in the manufacturer's full prescribing information brochure. Unused portions of the study drug will be discarded properly as per the institutional policies.

5.3. Intrathecal Dosage and Administration.
Patients will receive intrathecal chemotherapy as per standard of care. Methotrexate, Cytarabine, hydrocortisone, or a combination of these is allowed on the study. The number of lumbar punctures with Intrathecal chemotherapies will depend on the age of the patient, clinical status, comorbidities, etc and will be determined by the PI.

5.4. Venetoclax is commercially available. Commerical supply of each will be used. Detail product information may be found in the product prescribing information and available through the following links:

5. 4.1. Venetoclax:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208573s000lbl.pdf

5.5. Patients with PR or stable disease (SD) after the reinduction cycle may continue the treatment with the combination of CB-103 and venetoclax for a maximum of three additional cycles or until disease progression or bone marrow transplantation, whicher comes first.

6. DOSE MODIFICATIONS

6.1. Recommended CB-103 Dose Modification.

The follow-up evaluations for toxicities apply during or beyond cycle 1 of the study.

The following sections outline the specific dose modifications for CB-103 for non-haematologic toxicities and should be followed by the Investigator accordingly. One dose level reduction indicated in case of moderate/severe non-haematological toxicities in the following **Tables** corresponds to a 100mg reduction per dose of CB-103, e.g. from 500mg BID to 400 mg BID intermittent schedule.

As CB-103 and venetoclax do not have overlapping toxicity, dose modification of venetoclax is independent of CB-103 dose modification: treatment modifications for venetoclax related toxicities will be performed as per Venetoclax Summaries of product characteristics (SmPC).

6.1.1. Dose modification for renal toxicity (Table 7).

If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1, to allow for initiation of re-treatment and then at least weekly until either resolution or until stabilisation.

If proteinuria or haematuria ≥ CTCAE grade 2 or serum creatinine ≥ 2.0 x ULN has been demonstrated, a 24-hour urine collection must be obtained for total protein and total creatinine and must be repeated at least weekly until either resolution to baseline value to allow for initiation of re-treatment, or until stabilisation. Whenever a measured CrCl is obtained, a serum creatinine value should be obtained within ≤ 72 hours of the urine collection.

Table 7: Dose modifications for renal toxicities

Dose Modifications for CB-103	
Worst Toxicity CTCAE Grade unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Serum creatinine	
(< 2 x ULN)	Maintain dose level
(2 - 3 x ULN)	Omit dose administration until resolved to ≤ Grade 1, • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 - 6.0 x ULN) & Grade 4 (> 6.0 x ULN)	Omit dose administration and discontinue patient from study treatment

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal; ULN, upper limit of normal.
Grading according to NCI-CTCAE v.5.0 guideline.

6.1.2. Dose modification for liver toxicity (Table 8).

If bilirubin or AST/ALT > CTCAE grade 2 has been demonstrated, these parameters must be repeated at least twice a week until resolution to < CTCAE grade 1, to allow for initiation of re-treatment and then at least weekly until either resolution or until stabilisation.

Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinaemia should proceed as per the guidelines above, irrespective of the results of fractionation.

Table 8: Dose modifications for hepatic toxicities

Dose Modifications for CB-103	
Worst Toxicity CTCAE Grade unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Bilirubin	
Grade 1 (< 1.5 x ULN)	Maintain dose level
Grade 2 (1.5 - 3 x ULN)	Omit dose administration until resolved to ≤ Grade 1, • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3–0 - 10.0 x ULN)	Omit dose administration until resolved to ⩽ Grade 1, then ↓ 1 dose level
Grade 4 (> 10.0 x ULN)	Omit dose administration and discontinue patient from study treatment
AST or ALT	
Grade 1 (> ULN – 3.0 x ULN) & Grade 2 (>3.0 - 5.0 x ULN) without increase in total bilirubin >2 x ULN	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN) without increase in total bilirubin >2 x ULN	Omit dose administration until resolved to ≤ Grade 1 (or ≤ Grade 2 in case of liver metastasis), then • If resolved in ⩽ 7 days, then maintain dose level • If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without increase in total bilirubin >2 x ULN	Omit dose administration until resolved to ≤ Grade 1, then ↓ 1 dose level

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; LLN, lower limit of normal; PLT, platelets; ULN, upper limit of normal.
Grading according to NCI-CTCAE v.5.0 guideline.

6.1.3. Dose modification for eye toxicity (Table 9).

For toxicities related to visual symptoms related to CB-103, refer to the following table. In general, it is suggested that the patient avoids sudden exposure to bright sun light allowing time for possible delayed light accommodation.

Table 9: Dose modifications for ocular/vision related toxicities

Dose Modifications for CB-103	
Worst Toxicity CTCAE Grade unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Visual symptoms	
Grade 1	Maintain dose level
Grade 2	Omit dose administration until resolved to ≤ Grade 1 (or baseline), then continue treatment with CB-103 at the current dose level If visual symptoms ⩾ Grade 2 recur upon re-exposure to CB-103 and if is intolerable by patient, discontinue patient from study
Grade 3	Omit dose administration and discontinue patient from study
Grade 4	Omit dose administration and discontinue patient from study

Grading according to NCI-CTCAE v.5.0 guideline.

6.1.4. Dose modification for gastro-intestinal toxicities (diarrhoea) (Tables 10-11)

In non-clinical studies in different species (dog, rat, mouse), CB-103 administered at different doses and administration schedules did not show any gastro-intestinal toxicities, e.g. diarrhoea, weight loss. However, as other Notch inhibitors (GSIs, mABs) have shown diarrhoea as their major DLT, there might be a risk for CB-103 to also develop gastro-intestinal toxicities. In the event that diarrhoea is observed in clinical trial patients, the following algorithm for CB-103 dose modifications should be followed. Furthermore, section **6.1.7.** provides a management plan for the occurrence of diarrhoea with a description of measures and treatment suggestions.

Table 10: NCI CTCAE version 5.0 grading of diarrhoea

Grading	**0**	**1**	**2**	**3**	**4**	**5**
Diarrhoea	None	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline: limiting instrumental ADL	Increase of ≥7 stools per day over baseline; incontinence; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life- threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements.

Table 11: CB-103 Dose Modifications for Gastro-Intestinal Toxicity

Dose Modifications of CB-103 for Gastro-Intestinal Toxicity	
Worst Toxicity **CTCAE Grade unless otherwise specified (Value)**	**At any time during a cycle of CB-103** **(including intended day of dosing)**
Grade 1	Maintain dose level
Grade 2 (see section **6.1.7.** for treatment algorithm)	Omit dose administration until recovery to Grade 0 or baseline then continue at current dose level if grade 2 toxicity persisted for ≤ than 7 days. If grade 2 toxicity persisted for more than 7 days decrease dose by 1 dose level after resolution to Grade 0 or baseline
Grade 3 (see section **6.1.7.** for treatment algorithm)	Omit dose administration until recovery to Grade 0 or baseline then decrease the next scheduled dose by 1 dose level
Grade 4 (see section **6.1.7.** for treatment algorithm)	Omit dose administration until recovery to Grade 0 or baseline then decrease the next scheduled dose by 1 dose level* In the event Grade 4 toxicity lasts > 24 hours despite maximal medical attention discontinue treatment. If grade 4 toxicity lasts < 24 hours reduce dose by 1 dose level at next cycle If toxicity recurs discontinue treatment.
All grades	At the first sign of abdominal cramping, loose stools, or onset of diarrhoea, the patient should be treated according to section **6.1.7.** according to the recommended treatment algorithm. Omit dose administration of CB-103 for ≥ CTCAE grade 2 diarrhoea only if diarrhoea could not be controlled despite the use of optimal anti-diarrhoea treatments.

Grading according to NCI-CTCAE v.5.0 guideline.

6.1.5. Dose modification for cardiac toxicity (Table 12)

As in non-clinical studies with CB-103, QT prolongation was observed at higher doses and ECG changes in patients may be observed, therefore, intensive cardiac monitoring is implemented into this study with central management and review of multiple ECGs and Holter ECGs at selected timepoints. Furthermore ECHO/MUGA scans and cardiac markers will be assessed at selected time points. For toxicities related to QTc prolongation, refer to the table below.

The study treatment should be halted for any patient who experiences grade 4 QT prolongation (torsades or other related event) unless a clear alternative cause for the event can be identified and the event completely reverses with correction of the underlying issue.

Table 12: Dose modifications for cardiac abnormalities

Dose Modifications for CB-103	
Worst Toxicity **CTCAE Grade unless otherwise specified (Value)**	**At any time during a cycle of CB-103 (including intended day of dosing)**
Cardiac - Prolonged QTcF interval[2]	
During Cycle 1:	
Absolute QTcF< 450 ms	Maintain dose level and ECG monitoring as per visit schedule.
QTcF ≥ 450 ms and < 480 ms	Maintain dose level. ECG monitoring assessments should be increased as indicated (e.g. hourly until no QTcF ≥ 450 ms). Consider discontinuation of concomitant QT prolonging agents.
During any Cycle:	
Grade 3 or QTcF ≥ 480 ms as identified by the Investigator on the ECG.	Omit dose administration and recommend discontinuation of concomitant QT prolonging agents. Monitor patient with frequent ECGs as indicated (e.g. hourly) until the QTcF has returned to ≤ 450 ms. Further monitoring as clinically indicated. Exclude other causes of QTc prolongation such has hypokalaemia, hypo-magnesaemia and blood oxygenation status. Once QTcF prolongation has resolved, and if the QTcF prolongation was confirmed by central reading, patients may be re-treated at one lower dose level at the Investigator's discretion. ECG monitoring must continue throughout the treatment period as follows: • ECG monitoring assessments should be performed for 2 additional cycles at higher frequency as clinically indicated • If the ECGs obtained in the first additional cycle after dose reduction are without any QTcF prolongation, then ECG monitoring in subsequent cycles will be continued as per the visit schedule. • If the patient had an absolute QTcF ≥ 450 ms and < 480 ms, then ECG monitoring at a higher frequency will be continued for all subsequent cycles. • Patients who experience absolute QTcF ≥ 480 ms after one dose reduction will be discontinued from study.

Abbreviations: AE, adverse event; QTcF, corrected QT interval using Fridericia formula.
Grading according to NCI-CTCAE v.5.0 guideline.
[2]Exclude other causes of QTcF prolongation such has hypokalemia, hypomagnesemia and blood oxygenation status. Patients who develop hypokalemia or hypomagnesemia during the study should receive electrolyte replacement as soon as possible and should not receive further CB-103 dosing until the respective electrolytes are documented to be within normal limits.

6.1.6. Dose modification for non-laboratory toxicities (Table 13)

Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for retreatment, stabilisation of the toxicity, or study treatment completion.

Table 13: Dose modification for non-laboratory toxicities

Dose Modifications for CB-103 post cycle 1	
Worst Toxicity CTCAE Grade unless otherwise specified (Value)	**At any time during a cycle of CB-103 (including intended day of dosing)**
Non-laboratory AEs	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose administration until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4	Omit dose administration and discontinue patient from study

Grading according to NCI-CTCAE v.5.0 guideline.

6.1.7. Diarrhoea and Nausea Management Plan

Although no signs of gastro-intestinal toxicities (e.g., diarrhoea) were observed in the non-clinical safety and toxicology studies in different species (dog, rat, mouse) treated with CB-103 at different doses and administration schedules, the occurrence of diarrhoea cannot be excluded.

6.1.7.1. General measures:

- Stop all lactose-containing products, alcohol
- Stop laxatives, bulk fibre (e.g., Metamucil®, Procter & Gamble), and stool softeners (docusate sodium; Colace, Roberts)
- Drink 8 to 10 large glasses of clear liquids per day (e.g., water, Pedialyte® (Ross), Gatorade (Quaker), broth)
- Eat frequent small meals (e.g., bananas, rice, apple sauce, Ensure®, toast)
- Stop high-osmolar food supplements such as Ensure Plus and Jevity Plus (with fibre)

It is recommended that patients be provided loperamide tablets. It is mandatory that patients are instructed on the use of loperamide at cycle 1 in order to manage signs or symptoms of diarrhoea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hours (maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle and the investigational site should ensure that the patient understood the instruction. At the beginning of each cycle, each patient should be specifically questioned regarding any experience of diarrhoea or diarrhoea related symptoms. If symptoms were experienced, then the investigational site should question the patient regarding the actions taken for these symptoms.

6.1.7.2. Treatment of Diarrhoea Grade 1 or 2

Diarrhoea grade 1 or 2 will be treated with standard loperamide (initially at first administration 4 mg, then 2 mg every 4 hours [maximum of 16 mg/day] or after each unformed stool).

12-24 hours later:

Diarrhea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide after 12-hours diarrhoea-free interval

Diarrhea unresolved
Persisting diarrhoea grade 1 or 2 will be treated with addition of opium tincture, dihydrocodeine tartrate tablets/injections and start early on with corticosteroids which is the recommended treatment for the development of goblet cell metaplasia seen with other Notch inhibitors. Treatment should be accompanied by monitoring the patient's condition (to rule out dehydration, sepsis, ileus), medical check and selected workup. Observe patient for response to antidiarrheal treatment and may also consider treatment with high dose corticosteroids.
Persisting diarrhoea grade 3 or 4 may be treated with high dose loperamide (initially 4 mg, then 2 mg every 2 hours), addition of opium tincture or dihydrocodeine tartrate tablets/injections and with high dose corticosteroids to potentially inhibit the development of the goblet cell metaplasia seen with other Notch inhibitors. Furthermore, start of i.v. fluids, parenteral nutrition and antibiotics as needed with monitoring of patients' condition (to rule out dehydration, sepsis, ileus), medical check and workup (perform appropriate additional testing) should be started immediately. Observe patient for response.

After 12-24 hours:

Diarrhoea resolved

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Discontinue loperamide and/or other treatment after 12-hours diarrhoea-free interval

Diarrhoea unresolved

- If diarrhoea still persisting (NCI CTC grades 1 and 2), after 2 x 24 hours with high dose loperamide, opiates and corticosteroids then admit to hospital and employ measures as for grade 3 and 4 until diarrhoea resolved.
- If diarrhoea still persisting and progressed to NCI grades 3 and 4, employ measures described below.

6.1.7.3. Treatment of Diarrhoea Grade 3 or 4

Severe diarrhoea grade 3 or 4 may be treated with hospitalisation, high dose loperamide (initially 4 mg, then 2 mg every 2 hours, addition of opium tincture or dihydrocodeine tartrate tablets/injections as well as early start of administration of corticosteroids as being the recommended treatment for goblet cell metaplasia

observed in patients treated with other Notch inhibitors. Furthermore, start of i.v. fluids, parenteral nutrition and antibiotics as needed with monitoring of patients' condition (to rule out dehydration, sepsis, ileus), medical check and workup. Observe patient for response.

After 12-24 hours:

- If diarrhoea persisting administer high dose corticosteroids and consider subcutaneous (s.c.) Sandostatin/octreotide (100-500 µg three times daily [TID])
- Continue i.v. fluids, parenteral nutrition and antibiotics as needed
- If diarrhoea grade 3 or 4 still persists patients should receive besides corticosteroids opium tincture or dihydrocodeine tartrate injections s.c. or intramuscular (i.m.)
- If diarrhoea grade 3 or 4 is still persisting s.c. Sandostatin/octreotide (500-1000 µg TID) should be administered.
- To control and/or resolve diarrhoea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhoea resolved.

6.1.7.4. Diarrhea Workup

Perform appropriate tests (American Gastroenterological Association [AGA] Technical Review on the Evaluation and Management of Chronic Diarrhoea; Fine and Schiller, 1999).

Spot stool analysis

- Collect stool separating it from urine (special containers, analysis immediately, exceptionally freeze samples)
- Blood
- Faecal leukocytes (Wright's staining and microscopy) or
- C. difficile toxin
- Faecal cultures such as Shigella and pathogenic E. coli - enterotoxigenic, enterohaemorrhagic etc., possibly Aeromonas, Pleisiomonas (if suspected exposure to contaminated water)

6.2. Recommended Venetoclax Dose Modification.

Interrupt dosing, reduce number of days, or reduce dose for toxicities. Treatment modifications for venetoclax related toxicities will be performed as per the respective summaries of product characteristics (SmPC). As CB-103 and venetoclax do not have overlapping toxicity, dose modification of CB-103 is independent of venetoclax dose modification: treatment modifications for CB-103 related are described in **Section 6.1.**

See the following **Tables 14a and 14b** for dose modifications for hematologic and other toxicities related to **venetoclax**. For patients who have had a dosing interruption greater than 1 week reassess for risk of TLS to determine if reinitiation with a reduced dose is necessary.

Table 14a: Recommended Dose Modifications of Venetoclax for Toxicities[a]

Event	Occurence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose.
		For any events of clinical TLS[b], resume at a reduced dose following resolution.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, VENCLEXTA therapy may be resumed at the same dose. No dose modification is required. Consider decreasing treatment days.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in **Table 14b** when resuming treatment with Venetoclax after resolution. Consider decreasing treatment days. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with Venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, Venetoclax therapy may be resumed at the same dose. Consider decreasing treatment days.
	2nd and subsequent occurrences	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in **Table 14b** when resuming treatment with Venetoclax after resolution. Consider decreasing treatment days. A larger dose reduction may occur at the discretion of the physician.
Consider decreasing treatment days for those patients with toxicities. Treatment could be decreased from 28 days to 21, 14 or 7 days, depending on the PI. Discontinue venetoclax for patients who require dose reductions to less than 25% of the scheduled dose for more than 2 weeks. [a]Adverse reactions were graded using NCI-CTCAE v.5.0 guideline. [b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures.		

Table 14b: Dose reduction for toxicity during Venetoclax treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10

[a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.

7. CONCOMITANT THERAPY

Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea and intrathecal chemotherapy; however, the subject's medication record will contain a list of concomitant medications. All supportive measures consistent with optimal patient care should be provided throughout the study according to the departmental standards.

7.1. Allowed Concomitant Therapy: Prophylactic or therapeutic intrathecal therapy is allowed, if central nervous system leukemia involvement is diagnosed after enrollment in this clinical trial. The use of hematopoietic growth factors or transfusions is allowed. The use of hydroxyurea is permitted at any time during the study period for cytoreduction. Corticosteroids (e.g. for management of allergic reactions, prophylaxis, etc.) are also allowed. Use of other immunosuppressive therapy, e.g. tacrolimus, may be allowed at the disgression of the clinical provider. Other supportive care studies are allowed, even if under an IND.

7.2. Prohibited Concomitant Therapy: Patients may not receive other investigational anti-neoplastic therapy drugs, excluding therapy as described in previous Section "Allowed Concomitant Therapy". Patients may not receive radiotherapy during the study.

The following medications should be strictly prohibited during the study treatment period, unless there are no signs of QTc prolongation in scheduled EKG:

- Drugs with a known risk to induce Torsades de Pointes: All QT-prolonging drugs (see Table 1 in of **Appendix 1**) are prohibited for all patients until permanent discontinuation of study treatment.
- Drugs with a conditional risk to induce Torsades de Pointes: Any QT prolonging medication with a conditional risk of inducing Torsades de Pointes listed in Table 2 of **Appendix 1** are prohibited for all patients from screening through permanent discontinuation of study treatment, except for the assumptions described in **Section 6.1.7.** for the treatment of diarrhea and nausea. These exceptions must be discussed in advance with the Sponsor on a case-by-case basis.
- Warfarin and Coumarin-type anticoagulants within 1 week prior first CB-103 dose.

8. Visit schedule and study assessments

Written ICF for participation in the study must be obtained from the patient, signed and dated before performing any study procedure. Patients will be informed about the study drug and will receive pertinent information regarding the study objectives, possible benefits, and potential AEs.They will also receive information on the follow-up procedures and possible risks they will be exposed to. The ICF also informs patients about how biological samples will be obtained and collected and its legal implications. Patients are allowed to enter the study based on confirmation of the eligibility criteria (refer to inclusion and exclusion criteria in **Section 3.1.** and **Section 3.2.**) at screening/baseline.

Assessments scheduled for days 1 of each cycle must be performed within 48 hours prior to study treatment administration, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can continue. All examinations listed below will be performed according to the Schedule of Assessments outlined in **Table 16**.

All screening tests and evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria within 21 days prior to the first administration of study medication. Disease assessments, such as bone marrow samples (aspirate and/or biopsy), EKG and LVEF evaluation, such as ECHO/MUGA scan, available and performed as part of clinical practice prior to obtain the signature of the ICF, and within 21 days prior to treatment start, are accepted. Therefore, such evaluations are not required to be repeated during the screening period.

Patients should be admitted for Cycle 1 days 1-7 to monitor for any adverse events and for completion of study evaluations due on day 5. Patients may be discharged after the completion of study evaluations at the discretion of the treating physician if drug combination is being tolerated without need for close monitoring for adverse events and patient is clinically stable for safe discharge.

8.1. Medical History and Demographic Data: Medical history includes clinically significant diseases, surgeries, reproductive status, smoking history, use of alcohol and drugs of abuse, all medications (e.g., prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) and physical/occupational/exercise. Demographic data will include year of birth, sex and self reported race/ethnicity (collecting this information is essential in order to be able to evaluate the results of this study, for example, in the case of PK outliers or important between-patient differences in terms of treatment effect). Evaluation of the inclusion and exclusion criteria will be performed at the screening visit.

8.2. Disease History: The patients' disease history from the time of diagnosis (including any biomarker information and details regarding anti-neoplastic treatments they have received in the past) will be collected at screening. The exact parameters to be collected will be outlined on the respective screening eCRF pages. Disease history will be taken at the screening visit.

8.3. ECOG performance status: Performance status will be measured using the ECOG performance status scale (**Table 15a**). Patient's performance status should preferentially be assessed by the same person throughout the study.

Table 15a: ECOG performance status grading

Grade	Performance Status
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 workof a light or sedentary nature, i.e., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Upand about more than 50% of waking hours

3	Capable of only limited self-care, confined to bed or chair more than 50% of wakinghours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: http://www.ecog.org/general/perf_stat.html

Lansky scale may be used with adolescent of age ≤ 16 years (Table 14b). It is rated by parents based on their child's activity over the past week. Parents fill out the assessment based on the directions on the form, and the form is readministered over time to assess for changes in performance status.

Table 15b: Lansky performance status grading

Rating	Description
100	Fully active, normal
90	Minor restrictions with strenuous physical activity
80	Active, but gets tired more quickly
70	Both greater restriction of, and less time spent in, active play
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	Stuck in bed; needs help even for quiet play
20	Often sleeping; play is entirely limited to very passive activities
10	Does not play nor get out of bed
0	unresponsive

8.4. Vital signs and physical exam: Oral body temperature, respiratory rate, sitting blood pressure, and sitting heart rate will be obtained while the patient is in a semi-supine/supine position after resting for approx. 5 minutes. Vital signs should be measured prior to blood draw or at least 10 minutes after the last blood draw. Additional determinations include body height (only at **Screening**) and body weight.

A complete physical examination should include an examination of head, eyes, ears, nose, and throat, as well as cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. As part of the tumor assessment, physical exams should also include evaluation of presence and degree of increase of lymph nodes, hepatomegaly, and splenomegaly.

Eye examinations will be performed by an ophthalmologist during screening, at EOT, and in case of abnormalities at the safety follow-up visit. An extended eye examination including invasive ophthalmologic assessments should be performed by an ophthalmologist during the treatment period, in case significant abnormalities are experienced by the patient or seen by the study doctor at the regular eye evaluation as part of the physical examinations.

The following standard ophthalmological assessments performed by an ophthalmologist are recommended:

1. Visual acuity test
2. Intraocular pressure test
3. Slit-lamp test
4. Dilated fundus test
5. Colour-vision (Ishihara-plate) test

Additional assessments or tests may be conducted by an ophthalmologist as clinically indicated. Invasive ophthalmologic assessments such as electroretinography (ERG) may be conducted if feasible, at the discretion of the site and may be conducted at the time when visual symptom(s) are reported (if any).

For any significant abnormalities seen at the eye examination, all assessed parameters and findings should be documented in the respective eCRF pages and source documents.

8.5. Pregnancy tests and assessment of fertility: Only female patients of childbearing potential must undergo serum and urine pregnancy tests

8.6. Disease assessment: Disease assessment by bone marrow samples (aspirate and/or biopsy), cytogenetics and flow cytometry is done at baseline screening and at completion of each treatment cycle. A bone marrow biopsy and/or aspirate will be obtained to assess bone marrow cellularity and to determine the percentage of leukemic blasts, including assessment of minimal residual disease (MRD) to confirm remission status.

At the baseline assessment, bone marrow biopsy and/or aspirate is within 3 weeks and no less than 1 day before the first drug dose. Then on each cycle, patients are assessed for disease response by bone marrow biopsy and/or aspirate on day 28. If the blasts in bone marrow are <5% but marrow is hypocellular (cellularity $\leqslant$15%) on day 28 ($\pm$3 days), then a repeat bone marrow biopsy and/or aspirate is obtained 1 week later to assess response; if residual leukemia is present, repeated bone marrow biopsy and/or aspirate will be obtained as medically indicated.

Only for patients with extramedullary disease or as clinically indicated a PET-CT will be performed at baseline and if positive, also at end of the induction and of the reinduction cycles, and thereafter as clinically indicated. A time window of ± 3 days is allowed for the tumor assessments. A wider time window is allowed only at baseline; however, assessments should be performed as close as possible to the 1st drug administration and if feasible, not later than 3 weeks prior to the 1st drug administration

8.7. Cardiac Assessments

8.7.1 12-lead ECG: 12-lead ECG monitoring will be performed within 14 days before the start of treatment, at Cycle 1 Day 1 and Cycle 1 Day 5, and then at day 1 of all reinduction cycles and EOT.

- C1D1: pre-dose, 2-hours post-dose morning dose and 2-hours post-dose evening dose
- C1D5: 2-hours post-dose morning dose and 2-hours post-dose evening dose

8.7.2. Cardiac Imaging – ECHO or MUGA: monitoring will be performed within 14 days before the start of treatment, and then prior to day 1 of each subsequent cycle if clinically indicated based on the treating physician's assessment.

8.8. Pharmacokinetic Profile: Blood samples for determination of plasma concentrations of CB-103, will be collected as detailed below:

- C1D1: pre-dose, 2-, 6-hours post-dose morning dose and 2- hours post-dose evening dose (± 5 minutes)

- C1D5: pre-dose, 2-, 6-hours post-dose morning dose and 2- hours post-dose evening dose (± 5 minutes)

On the day of PK sampling the patient should be fasting: on that day, CB-103 will be taken together with the study staff with a glass of water. On Cycle 1 Day 1 food should be withheld for at least 3 hours after study drug intake. Water can be taken ad libitum. On Day 5 of Cycle 1, food consumption can be started after the second PK sample.

8.9. Laboratory assessments: The following laboratory tests will be performed within 48 hours prior Day 1 of each cycle: they do not need to be repeated at Cycle 1, Day 1 if they were performed at screening within 48 hours prior to start of study treatment. They may be performed at a local laboratory. For table of assessment and schedule, see **Table 16**.

Outside labs will be permitted and the PI/treating physician will review the labs for clinical significance, and sign/date the results. If patients present treatment-related toxicities, monitor blood counts and chemistries as clinically indicated. These tests should include:

8.9.1. Hematology: Complete blood counts (CBC), white blood count (WBC) with differential, unless WBC <0.5 $x10^9$/L (in which case differential not needed), hemoglobin, platelet count). Hematology assessments will be performed at least 2 times weekly during the first treatment cycle and at least 1 time weekly during each successive treatment cycle.

8.9.2. Coagulation: Prothrombin time (PTT) and activated partial thromboplastin time (aPTT)

8.9.3. Biochemistry: Clinical Chemistry includes albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), carbon dioxide (CO2), uric acid, calcium, chloride, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, direct bilirubin (if total bilirubin is elevated above the upper limit normal), total protein, blood urea nitrogen (BUN) and creatinine. Clinical Chemistry will be performed at least 2 times weekly during the first treatment cycle and at least 1 time weekly during each successive treatment cycle.

8.9.4. Pharmacodynamic/Biomarker Assessments: Serial blood, CSF, and bone marrow samples will be obtained if additional fluid is available to measure gene and protein expression levels of relevant pathways (e.g. NOTCH, BCL2) as well as for longitudinal monitoring of tumor evolution by NGS. Results will not be limiting for patient enrollment.
The samples will be analyzed by Cellestia and/or their designated laboratory (ies) from the list below:

- Cellestia R&D (Switzerland)
- SGS (Switzerland)

Blood and bone marrow samples are mandatory at baseline for local evaluation. For all patients, repeated blood sampling and bone marrow biopsy will also be taken at completion of induction, reinduction cycles ± 3 days, and at time of progression. An additional blood sample to monitor target engagement (PD) will also be collected on C1D5 at one of the PK sampling timepoints and Day 26 of all cycles of treatment. Except for the baseline, blood samples must be taken on the last week-day of CB-103 intake before the 2 days off treatment.

Details on sample collection requirements, preparation, processing, storage, and shipment will be provided in a separate laboratorymanual.

Changes to the sampling scheme may be implemented based on the emerging data. Any adjustment will be recorded in the study file and the total number of samples taken will not be exceeded.

8. STUDY CALENDAR (28 day Cycle)

Table 16: Study Calendar

	Screening	Treatment Period										End of Treatment Visit[16]	Follow-Up[17]
		Cycle 1				Cycle 2			From Cycle 3				
Day of cycle	-21 to -1	1[2]	5	26	28	1[3]	26	28	1[3]	26	28	1	
Assessments[1]													
Informed Consent	X												
Demographics with body height (cm)	X												
Medical History	X												
Disease history (including number of prior therapy regimens for ALL)	X												
Inclusion/Exclusion	X												
ID Panel	X[20]												
Pregnancy Test	X[4]	X[4]				X[4]			X[4]			X[4]	
Vital Signs and body measurements													
ECOG Performance Status	X	X				X			X			X	X
Weight (kg)	X	X				X			X			X	X
Physical Exam	X	X		X[3]		X	X[3]		X	X[3]		X	X
Eye examination (see Section 8.4)	X			X			X			X		X	X
Body Temperature	X	X				X			X			X	X
Respiratory rate	X	X				X			X			X	X
Cardiac assessments													
Blood Pressure	X	X		X		X	X		X	X		X	
12-Lead EKG	X[6]	X	X			X			X			X	
ECHO or MUGA	X[6]	X[5]				X			X			X	
Standard Laboratory Procedures													
Biochemistry[7-8]	X	X	X	X		X	X		X	X			
Hematology[7-9]	X	X	X	X		X	X		X	X			
Coagulation[10]	X	X	X	X		X	X		X	X			
Disease Assessment[11]	X	X[5]		X		X[11]	X		X[11]	X			X[18]
Pharmacokinetic profile[12]		X	X										
Biomarker Assessments[13]		X	X	X			X			X		X	
Lumbar puncture & CSF sampling[14]	X			X			X			X			
Concomitant Medications	X	X	X	X		X	X		X[15]	X[15]			
Adverse Events	X	X	X	X		X	X		X	X		X	X
Survival Status													X

1. Assessments scheduled on days of dosing should be done prior to administration of study drug(s), unless otherwise specified.
2. Screening assessments can be used as day 1 assessments of cycle 1 if done within the previous 72 hrs.
3. End of previous cycle assessments (Day 26) can be used as day 1 assessments if done within Day 26-29. If subsequent cycle is delayed, hematology, chemistry, and coagulation labs and physical exam assessments should be repeated on Day 1 of cycle.
4. For women of childbearing potential only. Serum pregnancy test must be performed within 24-48 hours before first study treatment. During the on-treatment period and at the EoT visit, urine pregnancy testing should be done as indicated in the table or whenever a pregnancy is suspected. Pregnancy and suspected pregnancy occurring while the patient is on study drug treatment or within 90 days after the last dose of CB-103 should be reported to the supporting company (Cellestia AG).
5. Screening assessments can be used as day 1 assessments if done within the previous 14 days.
6. EKG and LVEF assessment by ECHO or MUGA should be done within 14 days before first study treatment: these assessments may be repeated at the Investigator's discretion in case of signs or symptoms of cardiotoxicity. See Sections 8.7.1 and 8.7.2.
7. Tests will be performed at least 2 times weekly during the first treatment cycle and at least 1 time weekly during each successive treatment cycle. Outside labs will be permitted and the PI/treating physician will review the labs for clinical significance, and sign/date the results. If patients present treatment-related toxicities, monitor blood counts and chemistries as clinically indicated. This assessment does not need to be repeated at Cycle 1, Day 1 if it was performed at screening within 48 hours prior to start of study treatment.
8. Laboratory tests to be performed locally, within 48 hours before study visit (Day 1 of each cycle, including Cycle 1, Day 1) include albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), carbon dioxide (CO_2), uric acid, calcium, chloride, glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, direct bilirubin (if total bilirubin is elevated above the upper limit normal), total protein, blood urea nitrogen (BUN) and creatinine.
9. CBC (WBC with differential, unless WBC <0.5 x109/L in which case differential not needed, Hemoglobin, and Platelet count).
10. Prothrombin time (PTT), activated partial thromboplastin time (aPTT), and fibrinogen. This assessment does not need to be repeated at Day 1 of cycles if it was performed within 3 days prior.
11. Disease assessment:
    - Bone marrow samples (aspirate and/or biopsy), cytogenetics, and flow cytometry: screening assessment can be used as day 1 assessment of the induction cycle if done within the previous 3 weeks; end of previous cycle assessment can be used as day 1 assessment of the next cycle if done in +/- 3 days.
    - At the baseline assessment, bone marrow biopsy and/or aspirate is within 21 days and no less than 1 day before the first drug dose.
    - Patients are assessed for disease response by bone marrow biopsy and/or aspirate on day 28 (±3 days) induction and subsequent cycles. If the blasts in bone marrow are <5% but marrow is hypocellular (cellularity $\leqslant$15%) on day 26, then a repeat bone marrow biopsy and/or aspirate is obtained 1 week later to assess response; if no clear definition of response to therapy may be determined, repeated bone marrow biopsy and/or aspirate will be obtained as clinically indicated.
    - For patients with extramedullary disease a PET-CT will be performed at baseline and if positive, also at C1D26, and Day 26 of all subsequent cycles (±3 days). Assessments should be performed as close as possible to the 1st drug administration and if feasible, a wider time window is allowed only at baseline, not later than 14 days prior to the 1st drug administration.
12. PK time sampling: blood sampling will be collected as per the schedule and time window indicated below:
    - C1D1: pre-dose, 2-, 6-hour post-morning dose, 2- hour post evening dose (± 5 minutes)
    - C1D5: pre-dose, 2-, 6-hour post-morning dose, 2- hour post evening dose (± 5 minutes)

    PK Samples will be analyzed by a designated laboratory under Cellestia's responsibility.
13. Biomarker assessments: Serial blood and bone marrow samples will be obtained to measure gene and protein expression levels of relevant pathways (e.g. NOTCH, BCL2) as well as for longitudinal monitoring of tumor evolution by NGS if leftover sample is available. Baseline, at time of completion of induction (+/- 3 days), and reinduction cycles ± 3 days, and at time of progression. Additional blood samples will be collected on C1D5 and on Day 26 of all cycles for PD analysis by a designated laboratory under Cellestia's responsibility.
14. Lumbar puncture (T-ALL/T-LBL) for prophylactic intrathecal therapy: if prophylactic intrathecal therapy is foreseen by the treating physician, a lumbar puncture may be performed up to 3 days before the first dose of CB-103, and may be repeated at the discretion of the treating physician at the end of the first cycle and at the end of any subsequent cycles on or around day 28. If clinically feasible, one additional sample will be collected to determine the exposure of CB-103 in the CSF (this measurement will be done by a designated laboratory under Cellestia's responsibility).
15. For patients with PR or stable disease (SD) after the induction cycle(s) who may receive add-on selective therapy chosen by the investigator on the basis of the ongoing biomarker expression of the disease while continuing the treatment with the combination of CB-103 and venetoclax, the add-on therapy will be reported in details on the CRF.
16. EoT visit is to be done 5 days after the last dose of any study treatment, unless the patient starts any subsequent antitumor therapy (in which case the EoT visit should be performed before the start of the new therapy, whenever possible).
17 First follow-up visit will be 26 days after EoT (± 5 days), and every three months (± 14 days) thereafter, until EoS (i.e., death, patient's refusal, lost to follow-up) or study termination, whichever occurs first. Survival status and information on posterior antitumor therapies will be collected, telephone contact being acceptable.
18. If patient discontinued treatment without progression, tumor assessment will be done until progression or start of new antitumor treatment.
19. In case of relevant related toxicities (i.e., Grade>1), every 4 weeks until resolution or stabilization: information collected by telephone contact is acceptable.
20. Hepatitis B, C infection, and HIV will be obtained within 21 days of start of treatment.

8.10 Outside Physician Participation During Treatment

1. MDACC Physician communications with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record.
2. A letter to the local physician outlining the patient's participation in a clinical trial will request a local physician agreement to supervise the patient's care.
3. Protocol required evaluations outside MDACC will be documented by telephone, fax or email. The PI/treating physician must review the labs, determine clinical significance and sign and date the report.
4. A copy of the informed consent, treatment schema, and evaluation during treatment will be provided to the local physician.
5. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies, and documentation of any hospitalizations.
6. The home physician will be requested to report to the MDACC physician investigator all life-threatening events within 24 hours of documented occurrence.
8. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator or their representative prior to initiation and will be documented in the patient record.

9. RESPONSE DEFINITIONS

Because morphologic examination of the bone marrow during periods of hematopoietic recovery after intensive chemotherapy may be unreliable, a response will be based on blast percentage by flow cytometry. Flow cytometric assessment of response (MRD) should be performed at MDACC. Blast percentages determined by morphology can be used in cases where the sample submitted for flow cytometry evaluation is limited or hemodiluted. Patients will be considered evaluable for response if they have been administered greater than 50% of the dose of CB-103. Patients will be evaluable for safety if they have been administered 1 dose of CB-103.

9.1. Study Endpoints:

9.1.1. Primary Efficacy Analysis: Clinical activity of CB-103 in combination with venetoclax will be assessed based on the overall response rate (NCCN Guidelines 2021) [30].

9.1.2. Response Criteria T-ALL:

9.1.2.1. CR (Complete Remission): Absolute neutrophil count > 1.0 x 10^9/L, platelets > 100 x 10^9/L, red cell transfusion independence, and bone marrow with < 5% blasts. No evidence of extramedullary disease.

9.1.2.2. CRi (CR with incomplete blood count recovery): Bone marrow with < 5% blasts, with peripheral neutrophils of ≤ 1.0 x 10^9/L or platelets ≤ 100 x 10^9/L.

9.1.2.3. PR (Partial Remission): All of the hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to 5% to 25% in the bone marrow aspirate. No evidence of extramedullary disease.

9.1.2.4. Relapse: Subsequent appearance, after achievement of CR, of ≥ 5% blasts in the bone marrow with confirmation by flow cytometry or the development of extramedullary disease after achievement of CR.

9.1.3. Additional Response Criteria for T-LBL:

In patients with extramedullary disase, radiographic tumor response assessments will be based on CT/MRI/PET-CT scans throughout the study and response determined by Investigator per the revised recommendations for response assessment of NHL per "The Lugano Classification", reported in **Appendix 2** [31].

Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two 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 (eg, 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.

9.1.4. Response Criteria for CNS Disease:

9.1.4.1. CNS remission: achievement of CNS-1 status in a patient with CNS-2 or CNS-3 status at diagnosis.

9.1.4.2. CNS relapse: new development of CNS-3 status or clinical signs of CNS leukemia New development of CNS-2 status on 2 consecutive lumbar punctures (between 2–4 weeks apart) with confirmation by immunophenotyping or other molecular testing methods.

9.1.5. Secondary efficacy endpoints:

To assess whether the ORR to CB-103 in combination with Venetoclax is dependent on pre-treatment expression of Notch and/or BCL2 pathway, patients will be stratified according to the pre-treatment presence or absence of Notch and BLC2 expression. ORR will be evaluated in each of the four strata.

For each subject, minimal residual disease (MRD, presence of leukemic cells below the threshold of detection by conventional morphologic methods), duration of response, event-free survival, and overall survival will be calculated.

The depth of remission, i.e. detection of MRD, will be evaluated by PCR/NGS methods that can detect leukemic cells at a sensitivity threshold of at least $1x10^{-6}$ bone MNCs. Flow cytometry and/or molecular analysis with PCR methods that can detect leukemic cells at a sensitivity threshold of at least $1x10^{-4}$ bone marrow nuclear cells (MNCs) will also be performed.

The duration of response is defined as the number of days from the date of initial response (PR or better) to the date of first documented disease progression/relapse or death, whichever occurs first. Event-free survival is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented treatment failure, relapses from CR, or death from any cause, whichever occurs first, and will be calculated for all patients. In the event that neither disease progression nor death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last tumor assessment date. Overall survival is defined as the number of days from study enrollment to death due to any cause.

9.1.6. Exploratory endpoints:

9.1.6.1. CB-103 plasma concentrations, PK parameters (e.g., Cmax and AUC0-8) vs safety and/or efficacy

9.1.6.2. PD parameters, as for instance Notch and BCL2 expressionin pre- and post-treatment marrow samples.

9.1.6.3. the number and percentage of patients that are able to transition to HSCT in:

9.1.6.3.1. Either in the patients achieving CR after the induction and reinduction cycles;

9.1.6.3.2. Or in the patients with PR or stable disease (SD) after the induction and reinduction cycles.

9.2. Primary Safety Endpoints:

9.2.1. Primary Safety Analysis: The incidence rate, severity and relationship to CB-103 and/or venetoclax of adverse drug reactions and serious drug reactions according to common terminology criteria for adverse events (CTCAE) NCI CTCAE version 5.0.

The overall incidence and severity of all adverse events using Common Toxicity Criteria v 4.0.

9.2.2. Safety Definitions:

9.2.2.1. Adverse Event (AE):

An Adverse Event is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study treatment, whether or not it is considered to be study drug(s) related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of the study.

Attribution - the determination of whether an adverse event is related to a medical treatment or procedure.

- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s)

Medical conditions/diseases present before starting study drugs are only considered adverse events if they worsen after starting the study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy.

The severity of the adverse events (AEs) -The severity of the adverse events (AEs) will be graded according to the **National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V**5.0**.** Events not included in the NCI CTCAE will be scored as follows:

General grading:

- **Grade 1:** Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- **Grade 2:** Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3:** Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- **Grade 4:** Life Threatening: discomfort that represents immediate risk of death

RedCap will be used as the electronic Case Report Form (eCRF). The Investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled.

Adverse events will be captured per the phase II recommended guidelines

- Signs and symptoms relating to adverse event diagnoses will not be captured as individual events. (e.g. event of catheter related infection: redness, pain, swelling

at catheter site are signs and symptoms of the catheter related infection and thus will not be recorded as individual events).

- The maximum grade of the adverse event (AE) will be captured per course or protocol defined visit date. The start date will be recorded as when the AE first began or worsened from baseline, regardless of when the event was at its highest grade.
- An AE will be recorded as intermittent if the AE is not continuous but reoccurs at an irregular interval within a course.
- Hematologic adverse events will not be recorded or reported for studies in patients with any type of leukemia and/or related disorders, except for:
    a. Prolonged myelosuppression as defined by marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts).
    b. Hematologic events that result in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
- Abnormal laboratory values or test results will not be recorded or reported as adverse events unless it leads to therapeutic intervention, results in dose modification or interruption, or meets the protocol definition of a DLT or SAE.

Only the following AEs from the Adverse Event Record will be reported in the CRF:

- Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
- All serious adverse events regardless of attribution to the study drug(s).
- Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled. For non-MD Anderson laboratory results, the principal investigator (or physician designee) will review laboratory results, and sign and date the results.

Table **17**: Recommended Adverse Event Recording Guidelines

Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

9.2.2.2. Serious Adverse Event or Serious Adverse reaction (SAE) Reporting Requirements for M D Anderson Sponsor IND:

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Sponsor **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the INDSponsor. This may include the development of a secondary malignancy.
- The electronic SAE application (OnCore) will be utilized for safety reporting to the IND Sponsor and MD Anderson IRB.

- All events reported to the supporting company must also be reported to the INDSponsor.

9.2.2.3. Reporting to Cellestia:

The investigator has to report the SAE to the supporting company of the study, Cellestia, within 24hr after becoming aware of the event and regardless of the relationship. The Adverse Event Reporting Form must be completed and forwarded to HEMEX Pharmacovigilance.

Contact details for HEMEX Pharmacovigilance are as follows:
Email: safety@hemex.ch
Phone number: +41 61 927 28 00

Please note there are no AEs of Special Interest listed in the IB.

10. REGULATORY REQUIREMENTS

10.1. Informed Consent: Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study. Consented subjects will be registered in the institutional database CORe.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

Subjects must have signed and dated an IRB approved informed consent in accordance with regulatory and institutional guidelines. MD Anderson SOP 04 will be used to guide the consent process for any patients for whom English is not the preferred language. This written informed consent must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.

10.2. Independent Ethics Committee/Institutional Review Board: A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The Investigator should notify the IRB of deviations from the protocol or serious adverse events occurring at the site. The Investigator will be responsible for obtaining annual IRB approval/renewal throughout the duration of the study.

10.3. Subject Confidentiality and Data Security: The Investigator must ensure that the subject's confidentiality is maintained. Additionally, this protocol is reviewed by the MD Anderson DSMC. Subjects should be identified by their study number only and should be kept in strict confidence by the Investigator. In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

Participant confidentiality and privacy is strictly held in trust by the participating investigator, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency, as applicable.

All research activities will be conducted in as private a setting as possible.

10.3.1 Access to Study Records

Study records may be accessed by IRB approved study personnel, or authorized inspectors. The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

10.3.2 Methods of Storage of Study Records

All data collected from MDACC sources will be maintained on a password protected server compliant with HIPAA. Study staff will have role based restricted access to directories and files on the server, according to project responsibilities. Only those with data entry permissions can add records. The PI or a delegate will review the conditions under which data will be released to recipient- investigators. Each application for use will need IRB approval and consents, if appropriate. The level of identifiability will determine the process for review and approval as well as the way information is shared.

Any study data or records maintained in paper documents will be stored in the offices of the PI or other delegated study staff, in a locked cabinet or other comparable controlled environment, and will be accessible only to authorized study team members or authorized inspectors and will be available in the even of an audit/inspection.

10.3.3 Duration of Study Record Storage

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

10.3.4 Sharing of Study Records

There are no plans to share study data with entities external to MD Anderson Cancer Center, aside from authorized inspectors as applicable (i.e. authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product). If data will be shared, IRB approval will be sought, and applicable inter-institutional agreements executed, prior to data sharing.

10.4. Data and Safety Monitoring Plan

This monitoring plan will be used as a guideline for the review of protocols sponsored by The University of Texas M D Anderson Cancer Center. The purpose of the plan is to ensure that the rights and wellbeing of human subjects are protected; the conduct of the trial is in accordance with the protocol, regulatory requirements, and good clinical practices (GCP); and safety reporting to the Institutional Review Board (IRB) and Food and Drug Administration (FDA) is accurate and complete.

10.4.1. Monitoring Visit Intervals

- The Clinical Research Monitor (CRM) will notify the site in writing of planned visits and the purpose of the visit to ensure the availability of medical records, study personnel and regulatory documents (if they are scheduled for review). Subjects will be monitored 6 months from the time of consent or until 30 days after the last dose of study drug, whichever comes first.
- The initial monitoring visit will occur after the first subject/preselected has completed the first cycle of treatment.

• Interim site monitoring visits will be conducted every 8-12 weeks during the enrollment phase of the study. In the case of slow/halted enrollment, monitoring visits may be extended to every 6 months (see section 12 below).
• Additional monitoring visits may be conducted if: enrollment proceeds more rapidly than expected; data entry is not being completed in a timely manner, and/or; the site is not in compliance with the protocol, federal and state regulations, and GCP.

10.4.2. Enrollment
The research team will be responsible for screening and enrolling all subjects. During scheduled monitoring visits protocol eligibility will be reviewed for each pre-selected subject in order to verify all criteria were met, and the subject was eligible for study participation.

10.4.3. Monitoring Requirements
For this phase II trial 30% of the subjects enrolled for treatment will be monitored.
Additional subjects may be monitored as needed and determined by the sponsor.
When in-person visits are conducted, the Monitoring Visit Log will be signed and dated by the CRM and one representative from the research team. During remote monitoring visits, the Monitoring Visit Log will be signed and dated by the CRM and the attendance record from the query meetings (if a query meeting is necessary) will be saved. The signed log or attendance record will be maintained in the sponsor files. Any exceptions from above will be documented on the Monitoring Visit Log and clarified in the applicable monitoring visit report.

a) Source Document Verification
The Clinical Research Monitor will review source documentation to verify study procedures were conducted per protocol specifications. The medical record and other protocol-specific documentation will be routinely reviewed.

b) Informed Consent Process
It will be verified that the most current IRB-approved version of the informed consent document was used to obtain consent; and that all required signatures are present, and the signature dates precede the performance of any study-related procedures.

c) Study Product Accountability/Administration
The protocol treatment plan includes investigational products (CB-103 and Venetoclax) and standard of care intrathecal treatment. The CRM will only verify that the standard of care regimen was administered at the appropriate time point per protocol. Venetoxclax will be dispensed through commercial supply and only treatment compliance will be monitored. CB-103 will be dispensed through Investigational Pharmacy, and compliance and accountability will be reviewed during monitoring visits. The Investigational Pharmacy records pertaining to the CB-103 shipping, receipt, storage, return, and destruction will also be periodically reviewed.
The following investigational product documentation will be verified during scheduled monitoring
visits:
• Drug/product dosing and scheduling adheres to the protocol guidelines
• Dose reductions, escalations, and/or delays were completed per protocol, and documented in the medical record
• Drug/product compliance and accountability records are being maintained

10.4.4. Adverse Event Reporting

The Clinical Research Monitor will verify adverse events are collected/reported per protocol guidelines, graded using NCI Common Toxicity Grading Criteria, and attribution is assigned by the PI or designee; and ensure serious adverse events are reported per IND and IRB guidelines, and per any agreements with supporting companies.

10.4.5. Concomitant Medication

Concomitant hydroxyurea and intrathecal chemotherapy will be entered into the REDCap case report form.

10.4.6. Response

It will be verified that response assessments are obtained and documented, and the corresponding treatment decisions are in compliance with the protocol guidelines.

10.4.7. Data Recording

The REDCap database and OnCore will be utilized as the electronic case report form (eCRF) for this study. During monitoring visits key eCRF entries will be reviewed and compared with source documentation. This limited data review will include the eligibility criteria, adverse events, protocol treatment, and off-study summary. The Principal Investigator and research team will be responsible for ensuring all other data is entered per the protocol specifications, and the needs of the investigator.

10.4.8. Regulatory Document Review

Periodically throughout the course of the trial the regulatory files will be reviewed to ensure that the documentation is current, accurate and complete.

10.4.9. Queries/Findings

When issues are identified during the monitoring visit, queries will be generated on the query form and provided to the research team for response/resolution. The Clinical Research Monitor will attempt to meet with the research nurse and/or study/data coordinators at each visit, document discussions, and note any outstanding issues in a Follow-up Memo to the investigator. Resolution of all open queries will be requested prior to the start of the next monitoring visit.

10.4.10. Monitoring Reports/Follow Up Memo

A Monitoring Reports will be completed and saved in the sponsor files. The report will include, but is not limited to:

- Enrollment updates
- Informed consent
- Eligibility and supporting source documentation
- Status of limited case report form data entry
- Treatment and response
- Toxicity assessment and reporting
- SAE submissions
- Protocol compliance/protocol deviations and violations
- Compliance with all applicable regulations and GCP
- Concerns/issues expressed by study site personnel

Status of previously identified issues will be addressed in subsequent reports, including any actions or requests of the IND sponsor.

The research team will receive a Follow-up Memo to identify the issues noted during the monitoring visit (queries will be sent as an attachment as applicable) and state the plan for resolution of the open issues.

10.4.11. Deviations/Violations

The CRM will ensure that protocol deviations and violations are reported per the Investigator's interpretation of IRB policy. Deviations and violations will be documented in the Monitoring Report.

10.4.12. Monitoring Update Visits

When all monitoring has completed as outlined in the Monitoring Plan, or during periods of slow enrollment, the protocol can be transitioned to Monitoring Update status. A Monitoring Update report will be completed every 6 months until the closeout process has concluded (see section 13), or enrollment resumes. The report will include, but is not limited to the following:

- Enrollment status
- Subjects on active treatment or in follow up
- Protocol revisions since the last visit
- Re-consents for preselected subjects (as applicable)
- SAE submissions
- Changes with key study personnel

A Follow up Memo will be sent to the research team, which will include any outstanding issues noted during the Monitoring Update review.

10.4.13. Study Closeout

Once all subjects have been removed from the study a closeout visit will be conducted to ensure the regulatory documents are in order, and all closeout procedures are completed. Following an initial regulatory document review, the CRM will provide the research team with a summary of any outstanding items. Once all issues have been addressed and resolution verified, a Closeout Completion Memo will be provided to the investigator, and a Closeout Report will be completed for the sponsor files.

10.5. Study Termination: The investigators reserve the right to terminate the study according to the study contract. The Investigator should notify the IRB in writing of the study's completion or early termination. Subjects may be eligible for continued treatment off protocol and determined by the Principal Investigator.

11. TREATMENT DISCONTINUATION

Treatment will continue until discontinuation due to unacceptable toxicity, lack of response, relapse or progressive disease. This includes any of the following:

- Clinically significant progressive disease at any time.
- Death
- Possibility of undergoing allogeneic stem cell transplantation.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s), that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the Investigator, pose an unacceptable risk for the patient.
- Patient decision for study withdrawal.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the Investigator, sponsor, or any regulatory body.

Patients who discontinue treatment due to unacceptable toxicity, lack of response, relapse or progressive disease, or bone marrow transplantation are considered to have completed the study treatment per protocol. The patients need to complete End Of Treatment (EOT) visit.

Once a patient has discontinued the study treatment and has completed the EOT visit, the patient shall be followed-up for survival up to two years from enrollment onto the study: data on survival status and any new anti-cancer therapy may be collected by phone every 3 months for up to 2 years after study enrollment. In case of relevant related toxicities (i.e., Grade>1) occurring during survival follow-up, the relevant information will be collected every 4 weeks until resolution or stabilization of the event: information collected bytelephone contact is acceptable.

At disease progression or treatment discontinuation, the emergence of new neoplastic clones or further mutations during therapy with this combination shall be investigated by next generation sequencing (NGS) in peripheral blood mononuclear cells (PMBC) or, If available, bone marrow samples obtained from patients.

12. STATISTICAL CONSIDERATIONS

This is a phase II open-label single arm and single institution clinical trial to evaluate the efficacy and safety of CB-103 in combination with venetoclax in adolescent and adult patients with T-ALL/T-LL in first or second bone marrow recurrence refractory to initial induction therapy or refractory to at least one reinduction attempt. Up to 30 patients may be enrolled, without regard to Notch status; we anticipate that approximately 50% of these patients will be Notch positive. The primary efficacy endpoint of the study is overall response rate (ORR, including CR,CRi and PR rate) after the first two induction cycles, and the primary toxicity endpoint is the rate of toxic events, defined as a grade ≥3 non-haemtological AEs that are possibly or probably related to the study drugs (see Adverse Events (SAE) definition in section 9.2.2.1.) occurring during the 28 days of induction cycle.

We simultaneously monitor efficacy and toxicity using the Bayesian optimal phase 2 (BOP2) design [32]. Specifically, let n denote the interim sample size, and N denote the maximum sample size. Let Y_{eff} and Y_{tox} denote the binary efficacy and toxicity endpoints, with $Y_{eff} = 1$ and $Y_{tox} = 1$ indicating that patients experience efficacy and toxicity, respectively. We assume that the joint distribution of (Y_{eff}, Y_{tox}) follows a multinomial distribution with four elementary outcomes: (Y_{eff}, Y_{tox}) = (1, 1), (1, 0), (0, 1) and (0, 0). Let $\mathbf{p} = (P_{11}, P_{10}, P_{01}, P_{00})$ denote the probabilities of observing the four outcomes, and let $p_{eff} = Pr(Y_{eff} = 1)$, $p_{tox} = Pr(Y_{tox} = 1)$ and $p_{efftox} = Pr(Y_{eff} = 1, Y_{tox} = 1)$. When efficacy and toxicity endpoints are monitored separately, the joint distribution reduced to marginal distribution of efficacy and marginal distribution of toxicity, respectively.

The **treatment is deemed unacceptable if $\boldsymbol{p_{eff} \leq 0.15}$ or $\boldsymbol{p_{tox} > 0.20}$**. Thus, we will stop enrolling patients and claim that the treatment is unacceptable if

$$Pr(p_{eff} > 0.15|data) < \lambda\left(\frac{n}{N}\right)^{\alpha},$$

or

$$Pr(p_{tox} \leq 0.20|data) < \lambda\left(\frac{n}{N}\right)^{\alpha/3},$$

where λ=0.57 and α=0.86 are design parameters optimized to maximize the study power, i.e., probability of correctly concluding an efficacious and safe **treatment as acceptable when $\boldsymbol{p_{eff} = 0.3, p_{tox} = 0.10}$** and $p_{efftox} = 0.05$, while controlling that the probability of incorrectly claiming an inefficacious and toxic treatment, i.e., type I error, with $p_{eff} = 0.15$, $p_{tox} = 0.20$ and $p_{efftox} = \mathbf{0.05}$, to 8.3%. Note that in the safety stopping rule, the original publication of the design used the probability cutoff $\lambda(n/N)^{\alpha}$, here the attenuation factor 3 is added (i.e., $\alpha/3$) to obtain stricter interim stopping boundaries to enhance safety.

This optimization is performed assuming a vague Dirichlet prior Dir(0.05,0.1,0.15,0.7) for p. The prior is chosen such that it corresponds to a prior effective sample size of 1 patient, and the prior estimates of p_eff and p_tox match the values specified when the treatment is unacceptable. The above decision rule leads to the following optimal stopping boundaries:

Table 18: Optimized stopping boundaries

# patients treated	Stop if # response <=	OR # toxicity >=
10	0	3
20	2	5
30	5	6

When the total number of patients reaches the maximum sample size of 30, we conclude that the treatment is acceptable if the number of responses are greater than 5, and the number of toxicities are less than 6; otherwise we conclude that the treatment is unacceptable. The go/no-go criteria in Table 18 are non-binding.

Below (**Table 19**) are the operating characteristics of the design based on 10000 simulations using the BOP2 web application (BOP2 V1.4.10.0), which is available at http://www.trialdesign.org.

Table 19: Operating characteristics

Scenario	Pr(Eff)	Pr(Tox)	Pr(Eff & Tox)	Early Stopping (%)	Claim Acceptable (%)	Average Sample Size
1	0.30	0.2	0.05	48.77	33.34	21.7
2	0.15	0.3	0.05	89.47	1.56	14.2
3	0.30	0.1	0.05	14.26	77.76	27.6
4	0.15	0.1	0.05	51.07	20.83	22.3
5	0.30	0.2	0.10	49.39	31.94	21.6
6	0.15	0.2	0.05	71.48	8.34	18.2
7	0.20	0.1	0.05	31.75	45.19	25.1
8	0.15	0.4	0.06	97.62	0.19	11.6
9	0.40	0.1	0.06	9.74	86.76	28.3
10	0.40	0.4	0.16	96.03	0.50	12.1

Upon completion of the trial, efficacy (per ORR and toxicity rates will be summarized as proportions with corresponding 95% Agresti-Coull confidence intervals. Given 30 patients, the following table (**Table 20**) provides rates and confidence intervals over a range of incidences:

Table 20: Rates and Confidence Intervals

Incidence	Proportion (95% CI)
0/30	0 (0, 0.13)
1/30	0.03 (0, 0.18)
2/30	0.07 (0.01, 0.22)
3/30	0.1 (0.03, 0.26)
4/30	0.13 (0.05, 0.3)
5/30	0.17 (0.07, 0.34)
6/30	0.2 (0.09, 0.38)
7/30	0.23 (0.12, 0.41)

8/30	0.27 (0.14, 0.45)
9/30	0.3 (0.17, 0.48)
10/30	0.33 (0.19, 0.51)
11/30	0.37 (0.22, 0.55)
12/30	0.4 (0.25, 0.58)
13/30	0.43 (0.27, 0.61)
14/30	0.47 (0.3, 0.64)
15/30	0.5 (0.33, 0.67)
16/30	0.53 (0.36, 0.7)
17/30	0.57 (0.39, 0.73)
18/30	0.6 (0.42, 0.75)
19/30	0.63 (0.45, 0.78)
20/30	0.67 (0.49, 0.81)
21/30	0.7 (0.52, 0.83)
22/30	0.73 (0.55, 0.86)
23/30	0.77 (0.59, 0.88)
24/30	0.8 (0.62, 0.91)
25/30	0.83 (0.66, 0.93)
26/30	0.87 (0.7, 0.95)
27/30	0.9 (0.74, 0.97)
28/30	0.93 (0.78, 0.99)
29/30	0.97 (0.82, 1)
30/30	1 (0.87, 1)

In secondary analysis, ORR will be summarized separately by Notch status as proportions with corresponding 95% Agresti-Coull confidence intervals. The difference in ORR between Notch groups will be assessed by Fisher's exact test.

Other measures of response (CR, Cri, PR, relapse, radiographic tumor response, CNS remission, CNS relapse) and minimal residual disease (MRD) will be summarized as proportions with corresponding 95% Agresti-Coull confidence intervals.

Duration of Response (DoR), Overall Survival (OS), and event-free Survival (EFS) will be summarized using Kaplan-Meier methods.

In exploratory analyses, correlations between ORR and pharmacokinetic and pharmacodynamics markers will be summarized. Rates of patients transitioning to Hematopoietic stem cell transplant (HSCT) will be summarized. Endpoints may be further summarized separately by Notch status.

Additional statistical methods may be used.

The Investigator is responsible for completing an efficacy/safety summary reports and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval.

This should be submitted after the first 10 evaluable patients complete 1 cycle of study treatment, and every 10 evaluable patients, thereafter. Efficacy summary will be submitted for every 10 evaluable patients after they complete 2 cycles of therapy.

A copy of the safety summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Appendix 1 QT Prolonging Drugs with Risk of Torsades de Pointes.

Table 1 List of prohibited QT prolonging drugs with a known risk to induce Torsades de Pointes

Drug	QT risk (*)	Comment
Aclarubicin	Known risk for TdP	Not available in US
Amiodarone	Known risk for TdP	Females >Males, TdP risk regarded as low
Anagrelide	Known risk for TdP	
Arsenic trioxide	Known risk for TdP	
Astemizole	Known risk for TdP	Removed from US market
Azithromycin	Known risk for TdP	Females>Males
Bepridil	Known risk for TdP	Removed from US market; Females>Males
Cesium chloride	Known risk for TdP	
Chloroquine	Known risk for TdP	
Chlorpromazine	Known risk for TdP	
Chlorprotixene	Known risk for TdP	Not available in US
Cilostazol	Known risk for TdP	
Ciprofloxacin	Known risk for TdP	
Cisapride	Known risk for TdP	Removed from US market; Females>Males
Citalopram	Known risk for TdP	
Clarithromycin	Known risk for TdP	
Cocaine	Known risk for TdP	
Disopyramide	Known risk for TdP	Females>Males
Dofetilide	Known risk for TdP	
Domperidone	Known risk for TdP	Not available in the US
Donepezil	Known risk for TdP	
Dronedarone	Known risk for TdP	
Droperidol	Known risk for TdP	
Erythromycin	Known risk for TdP	
Escitalopram	Known risk for TdP	
Flecainide	Known risk for TdP	
Fluconazole	Known risk for TdP	
Gatifloxacin	Known risk for TdP	Removed from US market
Grepafloxacin	Known risk for TdP	Removed from US market
Halofantrine	Known risk for TdP	Not available in US; Females>Males
Haloperidol	Known risk for TdP	When given i.v. or at higher than recommended doses, risk of sudden death, QT prolongation and torsades increased
Hydroquinidine	Known risk for TdP	Not available in US
Hydroxychloroquine	Known risk for TdP	
Ibogaine	Known risk for TdP	Not available in US
Ibutilide	Known risk for TdP	Females>Males
Levofloxacin	Known risk for TdP	
Levomepromazine	Known risk for TdP	Not available in the US
Levomethadyl acetate	Known risk for TdP	Removed from US market

Drug	QT risk (*)	Comment
Levosulpiride	Known risk for TdP	Not available in US
Meglumine antimoniate	Known risk for TdP	Not available in US
Mesoridazine	Known risk for TdP	Removed from US market
Methadone	Known risk for TdP	Females>Males
Mobocertinib	Known risk for TdP	
Moxifloxacin	Known risk for TdP	
Nifekalant	Known risk for TdP	Not available in US
Ondansetron	Known risk for TdP	
Oxaliplatin	Known risk for TdP	
Papaverine HCl	Known risk for TdP	Intracoronary
Pentamidine	Known risk for TdP	Females>Males
Pimozide	Known risk for TdP	Females>Males
Probucol	Known risk for TdP	Removed from US market
Procainamide	Known risk for TdP	
Propofol	Known risk for TdP	
Quinidine	Known risk for TdP	Females>Males
Roxithromycin	Known risk for TdP	Not available in US
Sertindole	Known risk for TdP	Not available in US
Sevoflurane	Known risk for TdP	
Sotalol	Known risk for TdP	Females>Males
Sparfloxacin	Known risk for TdP	Removed from US market
Sulpiride	Known risk for TdP	Not available in US
Sultopride	Known risk for TdP	Not available in US
Terfenadine	Known risk for TdP	Removed from US market
Terlipressin	Known risk for TdP	Not available in US
Terodiline	Known risk for TdP	Not available in US
Thioridazine	Known risk for TdP	
Vandetanib	Known risk for TdP	

Source:
(*) Classification according to the Qtdrugs org advisory board of the Arizona CET. Updated versions of medications which may prolong the QTc interval may be found at the following website: https://crediblemeds.org/index.php/?cID=328

Table 2 List of QT prolonging drugs with a conditional risk to induce Torsades de Pointes

Drug	QT risk (*)
Abiraterone	Conditional risk for TdP
Amantadine	Conditional risk for TdP
Amisulpride (not available in the US)	Conditional risk for TdP
Amitriptyline	Conditional risk for TdP
Amphotericin B	Conditional risk for TdP
Amsacrine (not available in the US)	Conditional risk for TdP
Atazanavir	Conditional risk for TdP
Bendroflumethiazide or bendrofluazide	Conditional risk for TdP
Chloral hydrate	Conditional risk for TdP

Drug	QT risk (*)
Cimetidine	Conditional risk for TdP
Clofazimine	Conditional risk for TdP
Clomipramine	Conditional risk for TdP
Dilitazem	Conditional risk for TdP
Diphenhydramine	Conditional risk for TdP
Doxepin	Conditional risk for TdP
Eperisone (not available in the US)	Conditional risk for TdP
Esomeprazole	Conditional risk for TdP
Famotidine	Conditional risk for TdP
Fluoxetine	Conditional risk for TdP
Fluvoxamine	Conditional risk for TdP
Furosemide (frusemide)	Conditional risk for TdP
Galantamine	Conditional risk for TdP
Garenoxacin (not available in the US)	Conditional risk for TdP
Hydrochlorothiazide	Conditional risk for TdP
Hydroxyzine	Conditional risk for TdP
Indapamide	Conditional risk for TdP
Itraconazole	Conditional risk for TdP
Ivabradine	Conditional risk for TdP
Ketoconazole	Conditional risk for TdP
Lansoprazole	Conditional risk for TdP
Loperamide	Conditional risk for TdP
Metoclopramide	Conditional risk for TdP
Metolazone	Conditional risk for TdP
Metronidazole	Conditional risk for TdP
Nelfinavir	Conditional risk for TdP
Olanzapine	Conditional risk for TdP
Omeprazole	Conditional risk for TdP
Pantoprazole	Conditional risk for TdP
Paroxetine	Conditional risk for TdP
Piperacillin/Tazobactam	Conditional risk for TdP
Posaconazole	Conditional risk for TdP
Propafenone	Conditional risk for TdP
Quetiapine	Conditional risk for TdP
Quinine sulfate	Conditional risk for TdP
Ranolazine	Conditional risk for TdP
Risperidone	Conditional risk for TdP
Sertraline	Conditional risk for TdP
Solifenacin	Conditional risk for TdP
Telaprevir	Conditional risk for TdP
Torsemide (Torasemide)	Conditional risk for TdP
Trazodone	Conditional risk for TdP
Voriconazole	Conditional risk for TdP
Ziprasidone	Conditional risk for TdP

Source:
(*) Classification according to the Qtdrugs org advisory board of the Arizona CET. Updated versions of medications which may prolong the QTc interval may be found at the following website: https://crediblemeds.org/index.php/?cID=328

Table 3 List of QT prolonging drugs with a possible risk to induce Torsades de Pointes

Drug	QT risk (*)
Abarelix (not available in the US)	Possible risk for TdP
Alfuzosin	Possible risk for TdP
Alimemazine (not available in the US)	Possible risk for TdP
Apalutamide	Possible risk for TdP
Apomorphine	Possible risk for TdP
Aripiprazole	Possible risk for TdP
Artemether/Lumefantrine	Possible risk for TdP
Artenimol+piperaquine (not available in the US)	Possible risk for TdP
Asenapine	Possible risk for TdP
Atomoxetine	Possible risk for TdP
Bedaquiline	Possible risk for TdP
Bendamustine	Possible risk for TdP
Betrixaban	Possible risk for TdP
Bicalutamide	Possible risk for TdP
Bortezomib	Possible risk for TdP
Bosutinib	Possible risk for TdP
Buprenorphine	Possible risk for TdP
Cabozantinib	Possible risk for TdP
Capecitabine	Possible risk for TdP
Carbetocin	Possible risk for TdP
Ceritinib	Possible risk for TdP
Clotiapine (not available in US)	Possible risk for TdP
Clozapine	Possible risk for TdP
Cobimetinib	Possible risk for TdP
Crizotinib	Possible risk for TdP
Cyamemazine (not available in the US)	Possible risk for TdP
Dabrafenib	Possible risk for TdP
Dasatinib	Possible risk for TdP
Degarelix	Possible risk for TdP
Delamanid (not available in the US)	Possible risk for TdP
Desipramine	Possible risk for TdP
Deutetrabenazine	Possible risk for TdP
Dexmedetomidine	Possible risk for TdP
Dextromethorphan/Quinidine	Possible risk for TdP
Dolasetron	Possible risk for TdP
Efavirenz	Possible risk for TdP
Eliglustat	Possible risk for TdP
Encorafenib	Possible risk for TdP
Entrectinib	Possible risk for TdP
Epirubicin	Possible risk for TdP
Eribulin mesylate	Possible risk for TdP
Ezogabine (Retigabine)	Possible risk for TdP
Felbamate	Possible risk for TdP
Fingolimod	Possible risk for TdP

Drug	QT risk (*)
Fluorouracil (5-FU)	Possible risk for TdP
Flupentixol (not available in the US)	Possible risk for TdP
Gemifloxacin	Possible risk for TdP
Gilteritinib	Possible risk for TdP
Glasdegib	Possible risk for TdP
Granisetron	Possible risk for TdP
Hydrocodone - ER	Possible risk for TdP
Iloperidone	Possible risk for TdP
Imatinib	Possible risk for TdP
Imipramine (melipramine)	Possible risk for TdP
Inotuzumab ozogamicin	Possible risk for TdP
Isradipine	Possible risk for TdP
Ivosidenib	Possible risk for TdP
Ketanserin (not available in the US)	Possible risk for TdP
Lacidipine (not available in the US)	Possible risk for TdP
Lapatinib	Possible risk for TdP
Lefamulin	Possible risk for TdP
Lenvatinib	Possible risk for TdP
Leuprolide	Possible risk for TdP
Levetiracetam	Possible risk for TdP
Levoketoconazole	
Levomethadone (not available in the US)	Possible risk for TdP
Lithium	Possible risk for TdP
Lofexidine	Possible risk for TdP
Lopinavir/Ritonavir	Possible risk for TdP
Lumateperone	Possible risk for TdP
Lurasidone	Possible risk for TdP
Maprotiline	Possible risk for TdP
Melperone (not available in the US)	Possible risk for TdP
Mianserin (not available in the US)	Possible risk for TdP
Midostaurin	Possible risk for TdP
Mifepristone	Possible risk for TdP
Mirabegron	Possible risk for TdP
Mirtazapine	Possible risk for TdP
Necitumumab	Possible risk for TdP
Nicardipine	Possible risk for TdP
Nilotinib	Possible risk for TdP
Norfloxacin	Possible risk for TdP
Nortriptyline	Possible risk for TdP
Nusinersen	Possible risk for TdP
Ofloxacin	Possible risk for TdP
Oliceridine	Possible risk for TdP
Osilodrostat	Possible risk for TdP
Osimertinib	Possible risk for TdP
Oxytocin	Possible risk for TdP
Ozanimod	Possible risk for TdP
Paliperidone	Possible risk for TdP
Palonosetron	Possible risk for TdP

Drug	QT risk (*)
Panobinostat	Possible risk for TdP
Pasireotide	Possible risk for TdP
Pazopanib	Possible risk for TdP
Perflutren lipid microspheres	Possible risk for TdP
Perphenazine	Possible risk for TdP
Pilsicainide (not available in the US)	Possible risk for TdP
Pimavanserin	Possible risk for TdP
Pipamperone (not available in the US)	Possible risk for TdP
Pilsicainide (not available in the US)	Possible risk for TdP
Pitolisant	Possible risk for TdP
Ponesimod	Possible risk for TdP
Pretomanid	Possible risk for TdP
Primaquine phosphate	Possible risk for TdP
Promethazine	Possible risk for TdP
Prothipendyl (not available in the US)	Possible risk for TdP
Relugolix	Possible risk for TdP
Remimazolam	Possible risk for TdP
Ribociclib	Possible risk for TdP
Rilpivirine	Possible risk for TdP
Romidepsin	Possible risk for TdP
Rucaparib	Possible risk for TdP
Saquinavir	Possible risk for TdP
Selpercatinib	Possible risk for TdP
Siponimod	Possible risk for TdP
Sorafenib	Possible risk for TdP
Sunitinib	Possible risk for TdP
Tacrolismus	Possible risk for TdP
Tamoxifen	Possible risk for TdP
Tazemetostat	Possible risk for TdP
Telavancin	Possible risk for TdP
Telithromycin	Possible risk for TdP
Tetrabenazine	Possible risk for TdP
Tiapride (not available in the US)	Possible risk for TdP
Tipiracil and Trifluridine	Possible risk for TdP
Tizanidine	Possible risk for TdP
Tolterodine	Possible risk for TdP
Toremifene	Possible risk for TdP
Tramadol	Possible risk for TdP
Trimipramine	Possible risk for TdP
Tropisetron (not available in the US)	Possible risk for TdP
Valbenazine	Possible risk for TdP
Vardenafil	Possible risk for TdP
Vemurafenib	Possible risk for TdP
Venlafaxine	Possible risk for TdP
Voclosporin	Possible risk for TdP
Vorinostat	Possible risk for TdP
Zotepine (not available in the US)	Possible risk for TdP
Zuclopenthixol, Zuclopentixol (not available in the US)	Possible risk for TdP

Drug	QT risk (*)
Source: (*) Classification according to the Qtdrugs org advisory board of the Arizona CET. Updated versions of medications which may prolong the QTc interval may be found at the following website: https://crediblemeds.org/index.php/?cID=328	

Appendix 2 Revised Criteria for Response Assessment

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 (eg, 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
Non-measured 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)
Lymph nodes and extra-lymphatic 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	> 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 X 5 mm as the default value

Non-measured lesions **Organ enlargement** **New lesions** **Bone marrow**	findings indicate residual disease Not applicable Not applicable None 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	When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation Absent/normal, regressed, but no increase Spleen must have regressed by > 50% in length beyond normal None Not applicable
No response or stable disease **Target nodes/nodal masses, extranodal lesions** **Nonmeasured lesion** **Organ enlargement** **New lesions** **Bone marrow**	No metabolic response Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment Not applicable Not applicable None No change from baseline	Stable disease < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met No increase consistent with progression No increase consistent with progression None Not applicable
Progressive disease **Individual target nodes/nodal masses** **Extranodal lesions**	Progressive metabolic disease Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	Progressive disease requires at least 1 of the following PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by > 50% from PPD nadir and an increase in LDi or SDi from

Nonmeasured lesions **New lesions**	None New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	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 (eg, 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 non-measured lesions Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if <
Bone marrow	New or recurrent FDG-avid foci	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 New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; 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.

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 two 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 (eg, 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 (eg, 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 (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5-Point Scale (5PS): see next Table.

Score	18-FDG uptake
1	No uptake
2	≤ Mediastinal blood pool
3	>Mediastinum and ≤ liver
4	Moderately > liver at any site
5	Markedly[1]>liver at any site and/or new sites of disease
X	New areas of uptake unlikely to be related to lymphoma

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