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# Venetoclax in combination with a pediatric-inspired regimen for the treatment of newly diagnosed adults with Philadelphia chromosome-negative acute lymphoblastic leukemia

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**Venetoclax in combination with a pediatric-inspired regimen for the treatment of newly diagnosed adults with Philadelphia chromosome-negative acute lymphoblastic leukemia**

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**Short Title:** Venetoclax/CALGB 10403 newly diagnosed Ph- ALL

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**Authorship Contributions**

All authors reviewed, revised, and provided approval of the final draft of the manuscript. Specific areas of contribution were as follows: Concept: IA and VP; Study design of the study, conduct and supervision: IA, VP, MR, JZ; Patient recruitment, treatment and monitoring, IA, VA, AAribi, AK, HP, PK, HA, AB, SO, KSandhu, BB, A.S.A, MMAM, AS, IL, PB, SJF, AS, GM, VP; Collection and assembly of clinical data, MA, IL, MV, JD, JZ; Correlative studies, supervision LG, WS, CS; Execution, KShimamoto; Data analysis and interpretation, JZ, IA, CS; first draft of manuscript: IA, VP, MR, JZ, CS.

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## KEY POINTS

- The addition of venetoclax to a pediatric-inspired regimen was safe in adults with B-ALL
- The combination of venetoclax and chemotherapy led to encouraging MRD- rate post consolidation in high-risk B-ALL, including Ph-like

## ABSTRACT

BCL-2 protein overexpression, common in B-cell acute lymphoblastic leukemia (B-ALL), including the Philadelphia (Ph)-like subtype, mediates leukemic cell survival. We treated 24 patients with 14 days of BCL-2 inhibitor, venetoclax, 400 mg daily (dose level 1) during induction and consolidation cycles combined with the CALGB 10403 regimen in newly diagnosed adults with Ph-negative B-ALL. Median age was 31 (range: 18-53) years, 92% were Hispanic, and 12 (50%) patients had Ph-like ALL. No dose limiting toxicity occurred in the phase 1 part. Median times to neutrophil and platelet count recovery were 20 and 21 days from start of induction, respectively. The most common grade ≥3 treatment-related adverse events were leukopenia (96%), neutropenia (83%), anemia (83%), thrombocytopenia (79%), lymphopenia (71%), hyperbilirubinemia (38%), and elevated ALT (33%). One patient with non-Ph-like ALL died from asparaginase-associated pancreatitis, and 23 (96%) patients achieved complete remission (CR) or CR with incomplete count recovery (CRi) following induction with or without extended induction phase. Of 22 patients who started consolidation, 20 (91%) achieved negative minimal residual disease status (MRD-) (<0.01%) CR/CRi by flow cytometry. Of 12 patients with Ph-like B-ALL, 11 achieved MRD- status post consolidation, with only one patient having persistent MRD at 0.01%. At diagnosis, Ph-like B-ALL cases had a trend toward a greater BCL-2-dependency compared to non-Ph-like (p= 0.06). The addition of venetoclax to a pediatric-inspired regimen was safe in adults with B-ALL, leading to encouraging MRD- rate post consolidation in high-risk B-ALL, including Ph-like (NCT05157971).

**INTRODUCTION:**

The evolution of frontline treatment for pediatric acute lymphoblastic leukemia (ALL) represents a significant advancement, with the vast majority of children with ALL now expected to be cured.(1) In contrast, ALL during adulthood continues to carry considerably inferior outcomes with significant risk for treatment failure.(2) Applying pediatric-inspired regimens to younger adults with newly diagnosed ALL has demonstrated feasibility and has led to improved survival outcomes,(3-8) and nowadays, pediatric-inspired regimens are considered the preferred approach for younger and fit adults. Yet, certain subtypes of ALL confer poor outcomes even with the use of pediatric-inspired regimens, and Philadelphia (Ph)-like ALL represents one of the most challenging examples. (3, 8) Philadelphia-like ALL is a high-risk B-cell subtype that conveys resistance toward frontline chemotherapy, with higher rates of induction failure, persistent measurable residual disease (MRD) post induction and consolidation, higher incidence for relapse, and inferior survival outcomes compared to other B-cell subtypes.(3, 8-10) Ph-like ALL was identified by gene expression profiling and cases harbor recurrent genetic alterations that activate a variety of tyrosine kinases and cytokine receptors.(9, 11) While tyrosine kinase inhibitors (TKIs) have shown promising *in vitro* activity in selected genetic subtypes of Ph-like ALL,(9, 11, 12) clinical studies utilizing TKIs in Ph-like ALL have only demonstrated marginal benefit,(13, 14) rendering Ph-like ALL a disease with unmet therapeutic need. Despite the success with early introduction of blinatumomab in frontline therapy in ALL,(15) Ph-like had a higher rate of relapse and lower disease-free survival with this strategy as observed in the GIMEMA LAL2317 Trial.(16)

B cell lymphoma-2 (BCL-2) family proteins are important regulators of intrinsic apoptotic pathways. The BCL-2 family of genes encodes proteins that facilitate either pro-apoptotic or anti-apoptotic activity. Overexpression of pro-survival BCL-2 family proteins is one mechanism by which leukemic cells circumvent apoptosis, and BCL-2 overexpression is common in various subtypes of B-cell ALL, including Ph-like ALL. Venetoclax is a selective potent BCL-2 inhibitor that facilitates restoring the process of apoptosis by binding directly to the BH3 binding pocket of BCL-2, displacing pro-apoptotic proteins and thereby triggering mitochondrial outer membrane permeabilization and activation of caspases. In preclinical studies, venetoclax has shown significant activity across various leukemia subtypes, including ALL, and the combination of venetoclax with navitoclax or chemotherapy has produced promising activity in relapsed/refractory ALL.(17, 18)

Considering the non-overlapping anticipated toxicities apart from myelosuppression, we hypothesized that the addition of a short course of venetoclax to a pediatric-type frontline regimen would be safe and lead to improvement in MRD response for B-ALL, including Ph-like subtype. Early clearance of MRD serves as a robust surrogate for survival outcomes in ALL,(3, 19-21) and it enhances disease risk-stratification for high-risk patients to better tailor their consolidative approach. Here we conducted a phase 1 study with an expansion cohort investigating the safety and efficacy of combining venetoclax with the CALGB 10403 regimen in newly diagnosed adults with Ph-negative B-ALL (NCT05157971).

**METHODS:**

Study population:

This was a prospective, single-arm, single-center phase 1 study with an expansion cohort investigating the safety of combining venetoclax with induction and consolidation cycles of the CALGB 10403 regimen (NCT05157971). The study enrolled newly diagnosed adults [18-54 years] with Ph-negative B-ALL. To enrich the study cohort for Ph-like ALL, we excluded patients with *BCR::ABL1*, *KMT2A*-rearrangement, *TCF3::PBX1*, and *ETV6::RUNX1* subtypes. The rationale for excluding these rearrangements was the ability to identify their presence quickly pretreatment by fluorescence in situ hybridization (FISH) and they don't frequently overlap with concurrent Ph-like diagnosis. The Ph-like diagnosis was made based on the presence of diagnostic Ph-like fusions using accumulative results from RNA-seq, conventional cytogenetics, FISH, RT-PCR, and single nucleotide polymorphism (SNP) array studies as described before.(22) This research was approved by the City of Hope (COH) Institutional Review Board (IRB), COH IRB#21134, and all participants gave written informed consent. All human subjects research was conducted in accordance with the Declaration of Helsinki. The study was funded by Abbvie and COH. The study was designed and conducted, and data were analyzed by the investigators.

Study Design:

The primary objective of the study was the safety and feasibility of combining venetoclax with the CALGB 10403 regimen backbone during induction in newly diagnosed adults with Ph-negative B cell ALL, and to identify the maximum tolerated dose (MTD) of venetoclax in combination with the CALGB 10403 regimen **(Supplementary Table 1** and **Figure 1)**. Key secondary objectives included assessing complete remission (CR)/CR with incomplete count recovery (CRi)/CR with partial hematologic recovery (CRh) post induction with or without

extended induction, assessing MRD- CR/CRi rate post induction and consolidation in all patients and in patients with Ph-like ALL, and estimation of one-year overall survival (OS) and leukemia free survival (LFS). OS is defined the time from treatment starting date to the date of death or last contact, whichever came first. LFS is defined as the time from treatment starting date to the date of relapse or death or last contact, whichever came first. Non-event was right censored at last contact date.

An initial safety lead-in phase to determine MTD was conducted at dose level 1 (DL1) following the standard 3+3 design, with a single dose de-escalation. DL1 of venetoclax was 400 mg administered orally daily on days 1-14 of induction and consolidation, with ramp-up dosing during induction (Day 1= 100 mg, Day 2= 200 mg, Days 3-14= 400 mg/day). The rationale for choosing DL1 was based on available safety and efficacy venetoclax in combination data derived from AML studies. (23, 24) The study design included a DL -1 of 200 mg to be given with the same schedule if >33% dose limiting toxicity (DLT) occurred in the first 6 patients. Extended induction was administered to patients who achieved partial remission (PR) with induction but still had residual blasts >5%, and venetoclax was administered on days 1-7 during this cycle. We restricted venetoclax administration to only induction, extended induction if applicable, and consolidation cycles to avoid cumulative prolonged cytopenia and as we anticipated that the majority of Ph-like ALL patients will receive allogeneic HSCT post consolidation. Strong or moderate CYP3A4 inducers were not allowed within 14 days prior to day 1 of protocol therapy. Venetoclax dose was adjusted if moderate or strong CYP3A4 inhibitors were used during therapy. The dose of pegasparaginase was reduced to 1000 IU/$m^2$ for patients ≥40 years and/or patients with body mass index (BMI) of ≥30. For patients who were younger than 22 years, calaspargase pegol-mknl was used. The administration of granulocyte colony stimulating factors (G-CSF) was allowed during the treatment cycles. Following consolidation, the subsequent therapy was administered per the treating physician discretion and included continuing treatment on the CALGB 10403 regimen, blinatumomab and/or consolidation with allogeneic hematopoietic cell transplantation (alloHCT). Patients were followed for relapse and survival after completing the study treatment.

Statistical Analysis and Endpoints Definition

CR was defined as <5% lymphoblasts in the bone marrow (BM), and the absence of circulating lymphoblasts or extramedullary disease, and absolute neutrophil count (ANC) >1000 cells/uL and platelet count >100k/uL. CRi was defined as CR with either platelet count <100k/uL or/and ANC <1000/uL, and CRh was defined as CR with platelet count > 50k/uL and ANC >500/uL.(25)

MRD was evaluated using multicolor flow cytometry (MFC) at a reference laboratory (University of Washington). MRD-negativity was defined as leukemic cells representing <0.01% of total nucleated cells. The assay sensitivity is 0.01%. Data analysis was performed as of April 30, 2024, and all authors had access to the primary clinical trial data. Jianying Zhang, Ph.D., analyzed the data and authors had access to the primary clinical trial data.

Exploratory studies:

We performed BH3 profiling of pre-treatment leukemic blasts in order to infer selective antiapoptotic protein dependencies (BCL-2, BCL-xL, or MCL1) at baseline. Viably cryopreserved diagnostic BM aspirate specimens were thawed, and single cell suspensions were prepared. In this MFC-based functional assay, BH3 peptides binding different BCL-2 proteins were used: BAD (BCL-2, BCL-xL), HRK (BCL-xL), MS1 (MCL1). PUMA2A and alamethicin (ALA) were used as negative and positive controls, respectively. Cells were permeabilized with digitonin and mitochondrial outer membrane permeabilization was measured by intracellular cytochrome c staining. Clinical MFC data were used to identify leukemic blasts, which were gated in the $CD45^{dim}SSc^{low}CD19^{pos}$ population, and CD34 was added for $CD34^{pos}$ cases. BCL2-dependent mitochondrial depolarization was calculated by subtracting HRK peptide response from BAD peptide response.

Next generation sequencing (NGS)-based clonoSEQ assay (Adaptive Biotechnologies, Seattle, WA) was performed, when possible, on post-induction and post-consolidation bone marrow samples. IGH V(D)J NGS MRD results were normalized to residual clonal cells per million nucleated cells and negativity was defined as <0.0001%.

**RESULTS:**

Twenty-six patients consented to participation in the study; two were ineligible due to the subsequent finding of *BCR::ABL1* translocation. As of data cutoff on April 30th, 2024, accrual was completed with a total of 24 patients who initiated treatment between March 2022 and December 2023, including 6 patients in the phase 1 part of the study and 18 patients in the expansion cohort; all patients were treated at DL1. The median age was 31 (range: 18-53) years, including 9 (38%) patients who were older than 40 years. Nineteen patients were male, 22 (92%) patients were Hispanic, and the median BMI was 30 (range: 19-54). Twelve (50%) patients had Ph-like diagnostic fusions, including 11 patients with *CRLF2*-fusions (*IGH::CRLF2*= 8; *P2RY8::CRLF2*= 3), and 1 patient with *JAK2*-fusion (*JAK2::PAX5*), and half (n= 6) of all Ph-like ALL patients had detectable *JAK2* gain-of-function mutations. Among non-Ph-like ALL

patients, 3 patients harbored *PAX5*-alterations and 2 patients had IgH-translocations. Characteristics of patients with and without Ph-like ALL were comparable, with the exception of higher presenting white blood cell count (WBC) in Ph-like ALL patients. **Table 1** depicts the study patients characteristics. **Supplementary Figure 1** is an oncoprint showing the distribution of fusions and mutations in each cohort.

Safety

Only one death occurred on the study, in a patient with non-Ph-like ALL and a BMI of 54 who developed severe pancreatitis attributed to pegasparaginase and subsequently died on day 34 from the time of initiating induction as the result of multiorgan failure. The onset of pancreatitis occurred after completion of the venetoclax course.

The median time to count recovery with neutrophil count ≥1000/uL and platelet count ≥100 K/uL were 20 (range: 15-40) and 21 (range: 2-57) days from start of induction, respectively. The median time from initiating consolidation to start day 29 of consolidation was 29 (range: 29-43) days, including 70% of patients who had started day 29 with no delays.

Treatment-related adverse events (TRAEs) were reported in all patients. Grade ≥3 AEs at least possibly related to venetoclax and/or the CALGB 10403 regimen that occurred in ≥ 20% of evaluable patients during induction and/or consolidation were as follows: leukopenia (96%), neutropenia (83%), anemia (83%), thrombocytopenia (79%), lymphopenia (71%), hyperbilirubinemia (38%), elevated ALT (33%), elevated AST (21%) and nausea (21%) **(Table 2). Supplementary Table 2** depicts all grades TRAEs attributed to either venetoclax and/or CALGB 10403 regimen, and TRAEs attributed only to venetoclax.

Response and Outcomes

The one patient with pegasparaginase toxicity was unevaluable for response and died without disease assessment as mentioned in the safety section. The remaining 23 (96%) patients achieved CR/CRi (CR= 21; CRi= 2) after induction with or without extended induction, including 2 (9%) patients with Ph-like ALL, who achieved PR (5-10% residual blasts with complete count recovery) post induction and then attained CR following the extended induction phase. Eleven patients (48%) achieved MRD- (<0.01%) CR/CRi by MFC on day 29 post induction, and one additional patient who was MRD+ (at 0.05%) on day 29 converted

subsequently to MRD- on repeat BM biopsy 2 weeks later without interim therapy during a period of holding treatment for high-grade hyperbilirubinemia.

Post induction, one patient (non-Ph-like ALL) who experienced severe sepsis and achieved MRD- by MFC and IGH NGS MRD did not receive consolidation therapy on the study; instead, blinatumomab consolidation was administered per the treating physician discretion. There were 22 patients who started consolidation on the study and underwent post consolidation disease assessment, including 12 with Ph-like ALL and 10 with non-Ph-like disease. The overall MRD- rate after consolidation was 91% (20 out of 22), corresponding with 92% (n= 11) for Ph-like ALL and 90% (n= 9) for non-Ph-like. The only patient with Ph-like who had persistent MRD post consolidation had only 0.01% residual disease by MFC, and, interestingly, the IGH NGS MRD was negative. For the non-Ph-like ALL patient with persistent MRD post consolidation, the residual disease level was 0.05%. **Table 3** illustrates treatment response.

As an exploratory objective, MRD by IGH V(D)J NGS (ClonoSEQ) was successfully performed for 22 patients post induction and 21 patients post consolidation. Rates of MRD- by IGH MRD (<0.0001%) post induction and consolidation were 27% and 62%, respectively. Post-consolidation IGH NGS MRD-negative CR/CRi rates were 45% and 80% for Ph-like and non-Ph-like ALL, respectively.

Immediate treatments post induction and/or consolidation were as follows: 5 patients continued chemotherapy according to the CALGB 10403 regimen, 16 patients received blinatumomab with or without additional chemotherapy, one patient relocated to a different city and was lost to follow up, and one patient underwent alloHCT after consolidation. There were a total of 7 (30%) patients who underwent consolidation with alloHCT in first CR, 6 of them with Ph-like ALL disease.

With a median follow up of 11.8 (range: 1.1-24.7) months, only one Ph-like ALL patient with *P2YR8::CRLF2* relapsed concurrently in the central nervous system (CNS) and the BM while receiving chemotherapy after completing the study. No other deaths were observed besides the early mortality from asparaginase-induced pancreatitis. Estimated OS rate at 1 year was 96% (95% CI: 88-100%) (**Figure 2a**). Estimated LFS rate at 1 year was 91% (95% CI: 80-100%) **(Figure 2b).**

<u>BH3 profiling</u>

MFC based BH3 profiling was performed on 19 available pre-treatment bone marrow samples. Leukemic blasts were gated based on $CD45^{dim}$ $SSC^{low}$ pattern and staining with CD34 and CD19. BCL-2 dependence (assessed as BAD minus HRK peptide response) was observed in pre-treatment blasts from 11 patients, while 4 patients had blasts that displayed MCL1-dependent BH3 profile (**Figure 3a**). Blasts from the other four cases displayed resistance to treatment with BH3 peptides, and all four of these cases were refractory to therapy when assessed by IGH-based V(D)J NGS MRD post-induction. None of the 19 patients had BCL-xL dependence pre-treatment when assessed with HRK peptide response. At diagnosis, Ph-like ALL cases were more BCL2-dependent compared to non-Ph-like cases (p= 0.06) **(Figure 3b).**

**DISCUSSION:**

Here, we have shown the feasibility and safety of administering 14 days of venetoclax at a 400 mg daily dose during induction and consolidation of an established pediatric-inspired regimen, namely the CALGB 10403, in relatively young adults with newly diagnosed Ph-negative B-ALL.(3) The only death on the study was unrelated to venetoclax and attributed to asparaginase-induced pancreatitis that occurred three weeks after completing the venetoclax course in an obese patient with a BMI of 54. Venetoclax administration did not significantly delay count recovery following induction or during the first part of consolidation. These favorable safety findings were observed notwithstanding the high-risk characteristics of the study population, including the enrollment of not so young adults, as 38% were older than 40 years who were otherwise ineligible for the CALGB 10403 study,(3) and half of the study population were obese, an independent predictor for increased treatment-related morbidity and inferior survival outcomes observed in the CALGB 10403 study as well as other pediatric-inspired regimens.(3, 26-28)

Importantly, the addition of venetoclax to a pediatric-inspired regimen was associated with an outstanding MRD- CR/CRi rate by flow cytometry attained after consolidation in this population of high-risk B-ALL. This promising high rate of MRD- response was most notable among patients with Ph-like ALL, all of whom achieved MRD-negativity, apart from one patient who only had a low-level of residual disease at 0.01%. Ph-like ALL represents a true challenge with current frontline therapy using pediatric- or adult-type regimens, and innovative frontline approaches are urgently needed. In the GIMEMA LAL1913 study, 78%, 53% and 42% of Ph-like ALL patients had persistent MRD+ (≥0.01% by PCR for IG/TR gene rearrangement) at weeks 4, 10 and 16, respectively, despite the utilization of a pediatric inspired regimen.(8) In the CALGB 10403 study, aberrant *CRLF2* expression, indicating Ph-like disease, and obesity were the only

predictors for inferior disease-free survival in multivariable analysis. Furthermore, among patients who had attained MRD-negativity by quantitative clone-specific PCR for IgH or TCR rearrangement following induction in the CALGB 10403, only 11% had Ph-like signature. (3) MRD-response is a highly prognostic marker and a powerful surrogate for long term survival outcomes, surpassing most of other prognostics factors. Hence, achieving early MRD response could improve outcomes of high-risk ALL patients and may avert the need for early alloHCT. Furthermore, the incorporation of ultrasensitive MRD assessment with IGH V(D)J-based NGS has shown superiority over flow cytometry MRD in retrospective studies,(29, 30) and can further enhance patient risk stratification. In our study, we have observed a significant proportion of patients who cleared MRD by IGH NGS MRD, and therefore, these patients may be potentially cured with a non-transplant approach. These favorable outcomes could be the result of BCL2 dependency for newly diagnosed Ph-like ALL patients as we have shown in BH3 profiling, and sequential exposure to venetoclax early in therapy could have sensitized their disease toward multiagent chemotherapy.

Median follow up for our patients is short, with only one patient relapsing despite the fact that only 30% of responders underwent alloHCT, all except one being Ph-like. The high rate of blinatumomab utilization during consolidation in our study may have improved early survival outcomes. However, Ph-like ALL patients continued to have high risk for relapse (43%) and a lower disease-free survival notwithstanding the frontline use of blinatumomab in the GIMEMA LAL2317 study(16). Ph-like ALL is a heterogenous disease, and until now, the value of adding TKI to frontline therapy is being tested but reported data so far are not compelling.(13, 14)

Our study is limited by the relatively small number of Ph-like ALL patients. Furthermore, most of the enrolled patients were Hispanics, and for Ph-like ALL, the vast majority had *CRLF2*-rearrangement (91.7%). As this is not the normal genetic distribution for Ph-like ALL patients, it may hinder the generalization of our study findings to other populations. Additionally, the heterogeneity in post-consolidation therapy and the frequent use of post-consolidation blinatumomab may further impact the interpretation of long-term outcomes. Finally, while the original definition of Ph-like ALL was based on gene expression profiling, the method is not broadly utilized clinically or commercially. However, identifying characteristic fusions and RNA expression patterns of Ph-like ALL is widely accepted and is similar to our definition in this study.

In conclusion, the addition of short courses of BCL2 inhibitor to pediatric inspired regimens was associated with favorable safety profile and encouraging MRD response in high-risk ALL patients, including Ph-like ALL. Longer follow up is needed in our study to evaluate if

early favorable outcomes endure with time, and a larger confirmatory study to validate our findings, are warranted.

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## TABLES

**Table 1. Patient characteristics**

| | All patients (%) | Ph-like (%) | Non-Ph-like (%) |
|---|---|---|---|
| **Number** | 24 | 12 | 12 |
| **Median age (range), yrs** | 31 (18-53) | 31 (18-53) | 31.5 (18-44) |
| **≥ 40 yrs** | 9 (38) | 5 (42) | 4 (33) |
| **Sex** | | | |
| Male | 19 (79) | 10 (83) | 9 (75) |
| Female | 5 (21) | 2 (17) | 3 (25) |
| **Ethnicity** | | | |
| Hispanic | 22 (92) | 11 (92) | 11 (92) |
| Non-Hispanic | 2 (8) | 1 (8) | 1 (8) |
| **BMI** | 30 (19-54) | 30 (22-42) | 31 (19-54) |
| **WBC at diagnosis (range), K/uL** | 4 (0.19-276) | 20.6 (2.9-276) | 2.1 (0.19-5.6) |
| **CNS at diagnosis** | | | |
| CNS-1 | 22 (92) | 10 (83) | 12 (100) |
| CNS-2 | 2 (8) | 2 (17) | 0 |

**Table 2. Treatment-related AEs (TRAEs) ≥ grade observed in at least 10% of patients**

| Adverse event | Number | (%) |
|---|---|---|
| **Leukopenia** | 23 | 96 |
| **Anemia** | 20 | 83 |
| **Neutropenia** | 20 | 83 |
| **Thrombocytopenia** | 19 | 79 |
| **Lymphopenia** | 17 | 71 |
| **Hyperbilirubinemia** | 9 | 38 |
| **ALT elevation** | 8 | 33 |
| **AST elevation** | 5 | 21 |
| **Nausea** | 5 | 21 |
| **Hyperglycemia** | 4 | 17 |
| **Sepsis** | 4 | 17 |
| **Febrile neutropenia** | 3 | 13 |
| **Hypertriglyceridemia** | 3 | 13 |
| **Pancreatitis** | 3 | 13 |

**Table 3. Efficacy outcomes and disposition**

| | All patients (%) | Ph-like (%) | Non-Ph-like (%) |
|---|---|---|---|
| **Number** | 24 | 12 | 12 |
| **CR/CRi after induction/extended induction** | 23/24 (96) | 12/12 (100) | 11/12 (92) |
| **Patients required extended induction** | 2/24 (8) | 2/12 (17) | 0/12 (0) |
| **CR/CRi after consolidation** | 22/22 (100) | 12/12 (100) | 10/10 (100) |
| **Post induction MRD- (<0.01%)** | | | |
| By flow | 11/23 (48) | 2/12 (17) | 9/11 (82) |
| By IGH NGS | 11/22 (50) | 3/12 (25) | 9/10 (90) |
| **Post consolidation MRD- (<0.01%) rate** | | | |
| By flow | 20/22 (91) | 11/12 (92) | 9/10 (90) |
| By IGH NGS | 20/21 (95) | 11/11 (100) | 9/10 (90) |
| **Post consolidation MRD- by IGH NGS (<0.0001%)** | 13/21 (62) | 5/11 (45) | 8/10 (80) |
| **Allogeneic HCT in CR1** | 7/23 (30) | 6/12 (50) | 1/11 (9) |
| **Immediate post study treatment** | | | |
| Blinatumomab +/- chemo | 17 (74) | 10 (83) | 7 (64) |
| Chemotherapy | 4 (17) | 1 (8) | 3 (27) |
| AlloHCT | 1 (4) | 1 (8) | 0 |
| Lost of follow up | 1 (4) | 0 | 1 (9) |
| **Early death (within 60 days)** | 1 (4) | 0 | 1 (8) |
| **Relapse** | 1 (4) | 1 (8) | 0 |

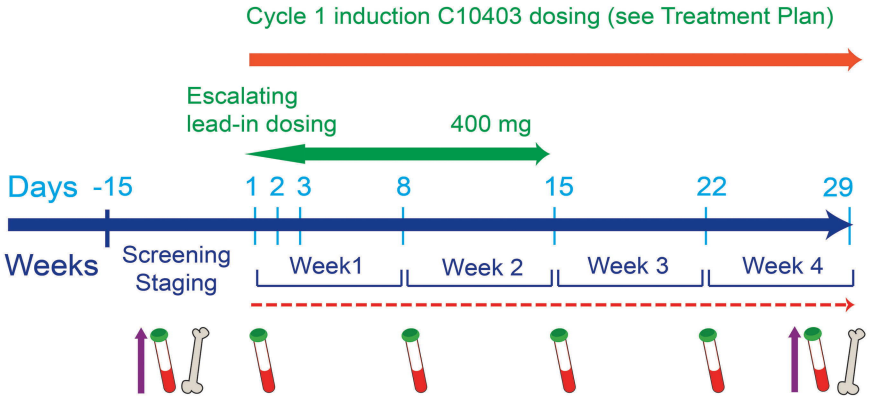
## FIGURE LEGENDS

**Figure 1. Study schema**

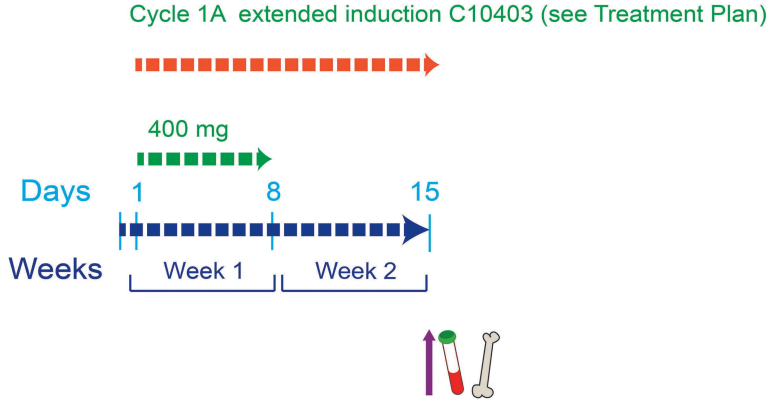
**Figure 2. Survival outcomes.** (a) OS; (b) LFS

**Figure 3. BH3 profiling.** (a) BCL2 dependence is measured by BAD-HRK response. PUMA2A is negative control; alamethicin is positive control. (b) Correlations between BCL2 dependency and Ph-like status (upper left figure), MCL1 dependency and Ph-like status (upper right figure), BCL2 dependency and post induction MRD status by flow cytometry (lower left figure), BCL2 dependency and post induction MRD status by IGH NGS (lower middle figure), and BCL2 dependency and post consolidation MRD status by IGH NGS (lower right figure).

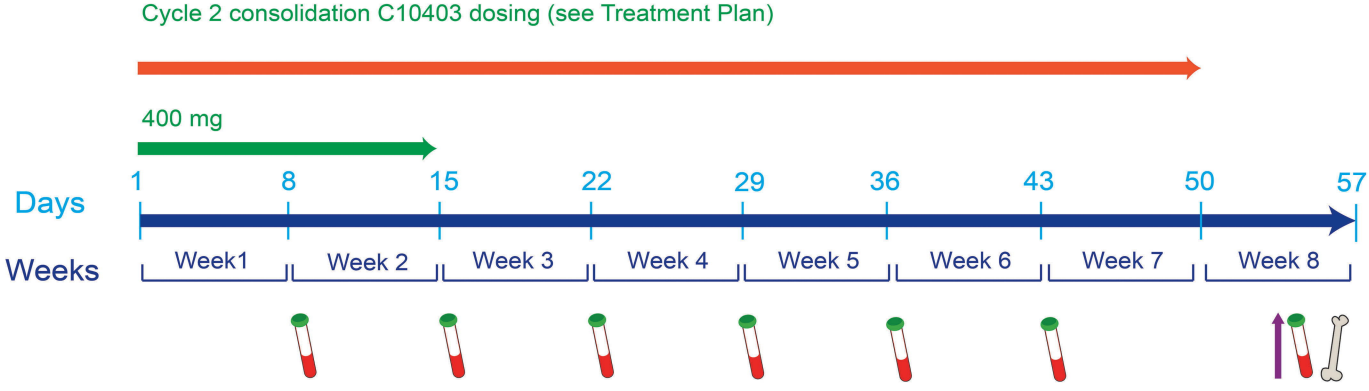

## Cycle 1: Induction



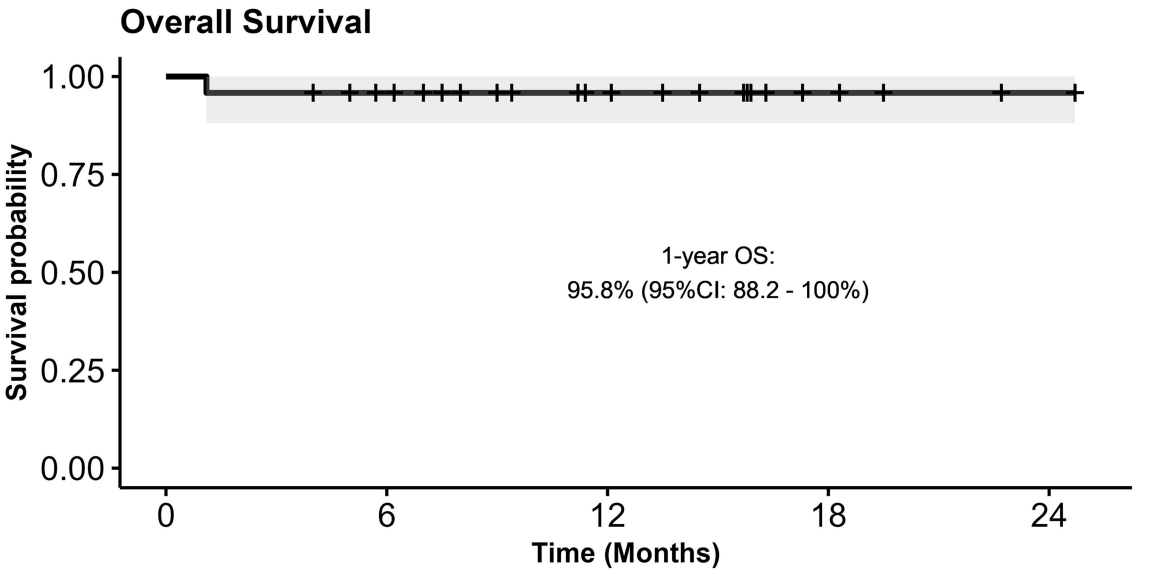

## Cycle 1A: Extended Induction for patients in PR or SD at week 4




## Cycle 2: Consolidation for patients with CR, CRi or CRh after Cycle 1 or 1A



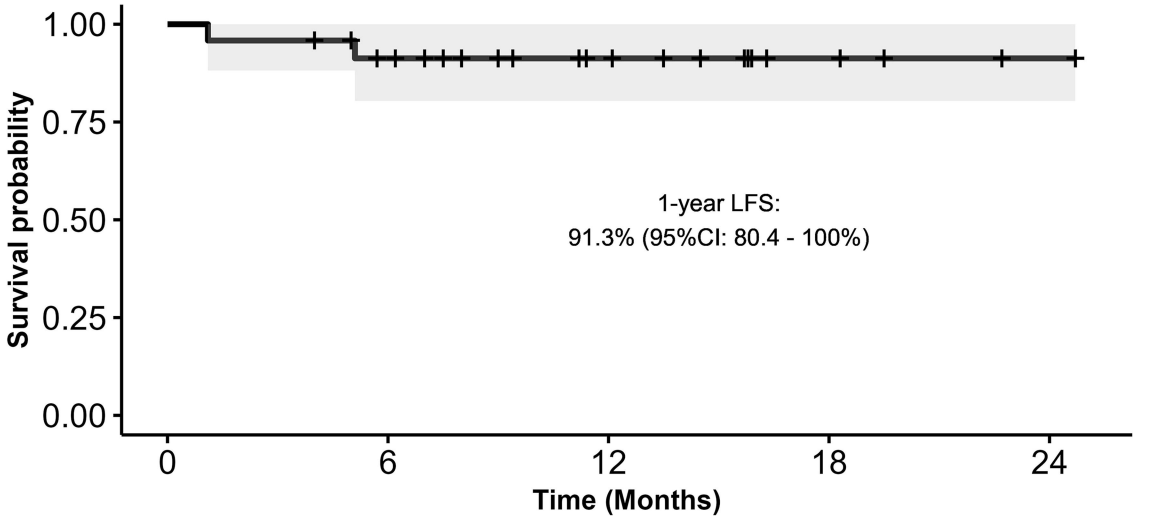
**a**




Number at risk: n (%)

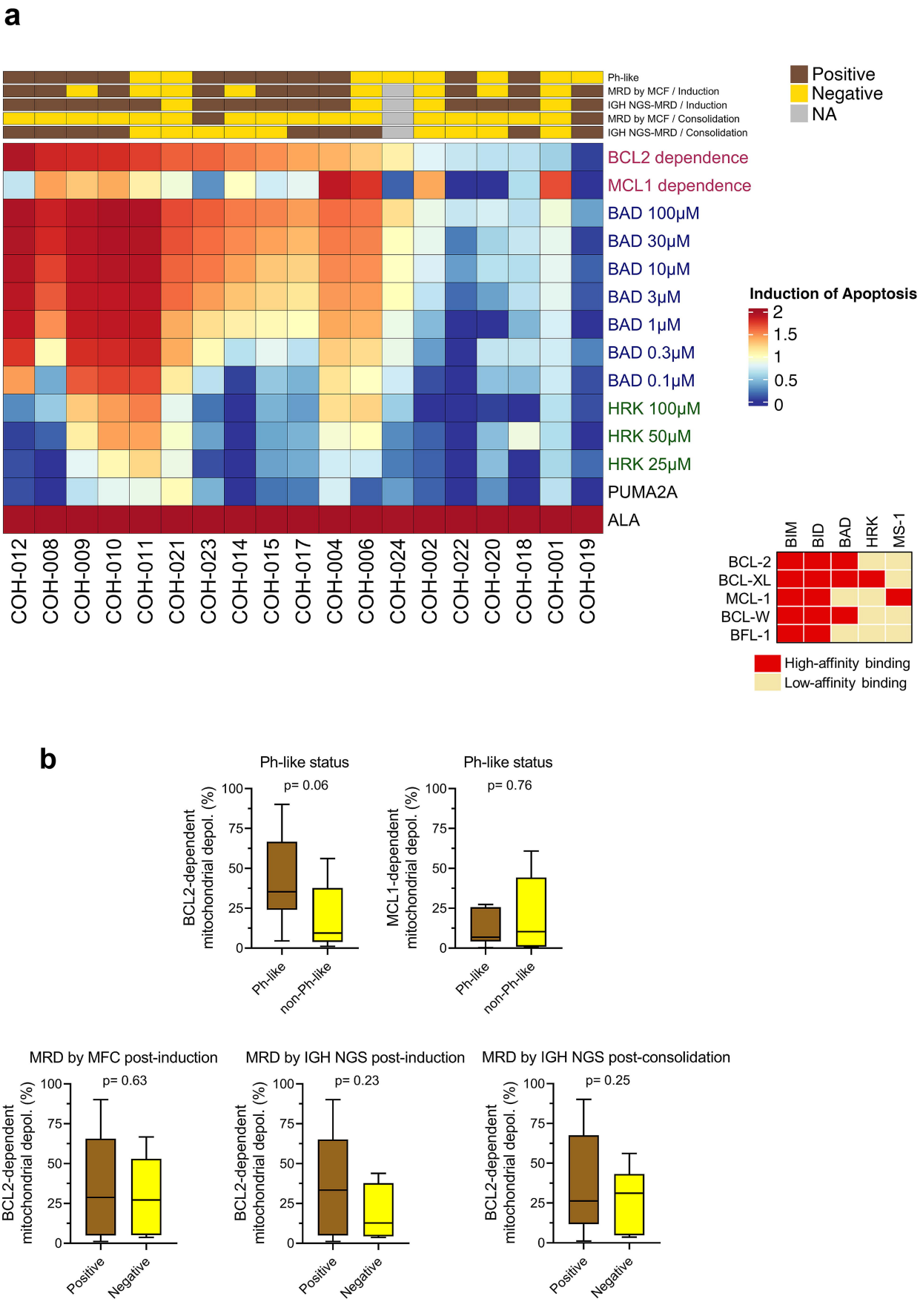
| | | | | | |
|---|---|---|---|---|---|
| All | 24 (100) | 20 (83) | 12 (50) | 4 (17) | 1 (4) |

**b**




Number at risk: n (%)

| | | | | | |
|---|---|---|---|---|---|
| All | 24 (100) | 19 (79) | 11 (46) | 4 (17) | 1 (4) |


a
Ph-like
MRD by MCF / Induction
IGH NGS-MRD / Induction
MRD by MCF / Consolidation
IGH NGS-MRD / Consolidation
Positive
Negative
NA
BCL2 dependence
MCL1 dependence
BAD 100µM
BAD 30µM
BAD 10µM
BAD 3µM
BAD 1µM
BAD 0.3µM
BAD 0.1µM
HRK 100µM
HRK 50µM
HRK 25µM
PUMA2A
ALA
COH-012
COH-008
COH-009
COH-010
COH-011
COH-021
COH-023
COH-014
COH-015
COH-017
COH-004
COH-006
COH-024
COH-002
COH-022
COH-020
COH-018
COH-001
COH-019
Induction of Apoptosis
2
1.5
1
0.5
0
BIM
BID
BAD
HRK
MS-1
BCL-2
BCL-XL
MCL-1
BCL-W
BFL-1
High-affinity binding
Low-affinity binding
b
Ph-like status
p= 0.06
BCL2-dependent mitochondrial depol. (%)
Ph-like
non-Ph-like
Ph-like status
p= 0.76
MCL1-dependent mitochondrial depol. (%)
MRD by MFC post-induction
p= 0.63
MRD by IGH NGS post-induction
p= 0.23
MRD by IGH NGS post-consolidation
p= 0.25
Positive
Negative

**Supplementary Table 1.** Treatment Regimen

Induction (Cycle 1)

| Drug | Route | Dosage | Days | Important Notes |
|---|---|---|---|---|
| Intrathecal Cytarabine (IT Ara-C) | IT | 70 mg | 1 | May be given prior to registration for patient convenience at the time of diagnostic bone marrow or venous line placement to avoid a second lumbar puncture. |
| Venetoclax *(INV)* | PO | 400 mg (dose level 1)<br>200 mg (dose level -1) | 1-14 | Ramp up dose level 1: 100 mg on Day 1, 200 mg on Day 2, 400 mg on Day 3 then daily to Day 14.<br>Ramp up dose level -1: 50 mg on Day 1, 100 mg on Day 2, 200 mg on Day 3 then daily to Day 14.<br>Appropriate dose adjustments will be made for concomitant use of CYP3A4 inhibitors (see **Section 7.3**). |
| Prednisone | PO | 30 mg/m$^2$/dose BID | 1-28 | Total daily dose: 60 mg/m2/day.<br>May give IV methylprednisolone at 80% of PO prednisone dose. |
| Vincristine | IV | 1.5 mg/m$^2$ | 1, 8, 15 & 22 | Maximum dose: 2 mg |
| Daunorubicin | IV | 25 mg/m$^2$ | 1, 8, 15 & 22 | |
| PEGaspargase* | IM or IV | 2000 IU/m$^2$ | 4 | *Calaspargase pegol may be utilized instead of PEGaspargase only for age < 22 years (described below). **Patients ≥ 22 y.o. must receive PEGaspargase.**<br>Maximum dose: 3750 IU<br>Dose delay to day 15 on PI discretion.<br>For patients with BMI ≥ 30 Kg/m$^2$ or age ≥ 40 years, the dose will be 1000 IU/m$^2$<br>Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to PEGaspargase.<br>Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity. |
| Calaspargase pegol* | IV | 2,500 units/m$^2$ | 4 | ***Calaspargase pegol** may be utilized instead of PEGaspargase **ONLY for age < 22 years**. Patients ≥ 22 y.o. must receive PEGaspargase as described above.<br>Maximum dose: 3750 IU<br>Dose delay to day 15 on PI discretion.<br>For patients with BMI ≥ 30 Kg/m$^2$, the dose will be 1000 IU/m$^2$<br>Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to calaspargase pegol.<br>Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity. |
| Intrathecal Methotrexate (IT MTX) | IT | 15 mg | 8, 15*, 22* & 29 | *CNS3 patients only<br>Send CSF for cell count and cytospin.<br>Patients should remain in a horizontal position for at least 60 mins following administration of IT chemotherapy to enhance drug delivery to the head. |

***Either PEGaspargase OR calaspargase pegol to be used depending on age of patient.**

- Calaspargase pegol < 22 years

- PEGaspargase ≥ 22 years

**Extended Induction (if required) (Cycle 1A)**

Extended Remission Induction Therapy is intended ONLY for patients with Day 29 M2 marrow (>5% lymphoblasts). Patients meeting these criteria are to begin Course 1A as soon as possible.

| Drug | Route | Dosage | Days | Important Notes |
|---|---|---|---|---|
| Venetoclax (INV) | PO | 400 mg (dose level 1)<br>200 mg (dose level -1) | 1-7 | Appropriate dose adjustments will be made for concomitant use of CYP3A4 inhibitors (see **Section 7.3**). |
| Prednisone | PO | 30 mg/m$^2$/dose BID | 1-14 | Total daily dose: 60 mg/m2/day.<br>May give IV methylprednisolone at 80% of PO prednisone dose. |
| Vincristine | IV | 1.5 mg/m$^2$ | 1 & 8 | Maximum dose: 2 mg |
| Daunorubicin | IV | 25 mg/m$^2$ | 1 | |
| PEGaspargase* | IM or IV | 2000 IU/m$^2$ | 4 | *Calaspargase pegol may be utilized instead of PEGaspargase only for age < 22 years (described below). **Patients ≥ 22 y.o. must receive PEGaspargase.**<br>Maximum dose: 3750 IU<br>For patients with BMI ≥ 30 Kg/m$^2$ or age ≥ 40 years, the dose will be 1000 IU/m$^2$<br>Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to PEGaspargase.<br>Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity. |
| Calaspargase pegol* | IV | 2,500 units/m$^2$ | 4 | ***Calaspargase pegol** may be utilized instead of PEGaspargase **ONLY for age < 22 years.** Patients ≥ 22 y.o. must receive PEGaspargase as described above.<br>Maximum dose: 3750 IU<br>Dose delay to day 15 on PI discretion.<br>For patients with BMI ≥ 30 Kg/m$^2$, the dose will be 1000 IU/m$^2$<br>Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to calaspargase pegol.<br>Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity. |

***Either PEGaspargase OR calaspargase pegol to be used depending on age of patient.**

- Calaspargase pegol < 22 years
- PEGaspargase ≥ 22 years

**Consolidation (Cycle 2)**

Patients must begin remission consolidation therapy within 7 days from remission marrow or when peripheral blood counts recover with ANC ≥ 750/µL and platelets ≥ 75,000/µL, whichever is later.

Therapy should be interrupted for patients who are febrile, neutropenic and proven infected, and resumed at the same point when the signs of infection have abated. Otherwise, therapy should not be interrupted for myelosuppression alone except on Day 29. Hold Day 29 chemotherapy until ANC ≥ 750/µL and platelets ≥ 75,000/µL.

| Drug | Route | Dosage | Days | Important Notes |
|---|---|---|---|---|
| Venetoclax (INV) | PO | 400 mg (dose level 1)<br>200 mg (dose level -1) | 1-14 | Appropriate dose adjustments will be made for concomitant use of CYP3A4 inhibitors (see **Section 7.3**). |
| Cyclophosphamide | IV | 1000 mg/m$^2$ | 1 & 29 | |

| | | | | |
|---|---|---|---|---|
| Cytarabine | IV or SC | 75 mg/m$^2$ | 1-4, 8-11, 29-32 & 36-39 | |
| Mercaptopurine (6-MP) | PO | 60 mg/m$^2$ | 1-14 & 29-42 | Take at the same time each day.<br>See Section 7.3 for dose adjustments based on TMPT status.<br>Adjust dose using 50 mg tablets and different doses on alternating days in order to attain a weekly cumulative dose as close to 420 mg/m$^2$/week as possible. Do not escalate dose based on blood counts during this course. |
| Vincristine | IV | 1.5 mg/m$^2$ | 15, 22, 43 & 50 | Maximum dose: 2 mg |
| PEGaspargase* | IM or IV | 2000 IU/m$^2$ | 15 & 43 | *Calaspargase pegol may be utilized instead of PEGaspargase ONLY for age < 22 years (described below). **Patients ≥ 22 y.o. must receive PEGaspargase.**<br>Maximum dose: 3750 IU<br>For patients with BMI ≥ 30 Kg/m$^2$ or age ≥ 40 years, the dose will be 1000 IU/m$^2$<br>Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to PEGaspargase.<br>Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity. |
| Calaspargase pegol* | IV | 2,500 units/m$^2$ | 15 & 43 | ***Calaspargase pegol** may be utilized instead of PEGaspargase **ONLY for age < 22 years.** Patients ≥ 22 y.o. must receive PEGaspargase as described above.<br>Maximum dose: 3750 IU<br>Dose delay to day 15 on PI discretion.<br>For patients with BMI ≥ 30 Kg/m$^2$, the dose will be 1000 IU/m$^2$<br>Pre-medicate with acetaminophen 650 mg, hydrocortisone 100 mg, diphenhydramine 25-50 mg and famotidine 20 mg equivalent prior to calaspargase pegol.<br>Observe for 1 hour (or per institutional standards) after infusion for signs of hypersensitivity. |
| Intrathecal Methotrexate (IT MTX) | IT | 15 mg | 1, 8, 15* & 22* | *Omit dose on Days 15 and 22 for CNS3 patients.<br>Send CSF for cell count and cytospin.<br>Patients should remain in a horizontal position for at least 60 mins following administration of IT chemotherapy to enhance drug delivery to the head. |

***Either PEGaspargase OR calaspargase pegol to be used depending on age of patient.**

- Calaspargase pegol < 22 years
- PEGaspargase ≥ 22 years

**Supplementary Table 2.** All Grades and ≥ Grade 3 at Least Possibly Related Treatment Related Adverse Events (TRAE) to Either Study Drug and All Grades at Least Possibly Related TRAE to Venetoclax

| Adverse Event | All Grades: AE at Least Possibly Related to Either Study Drug | | All Grades : AE at Least Possibly Related to Venetoclax | | Grade 3 or Higher: AE at Least Possibly Related to Either Study Drug | |
|---|---|---|---|---|---|---|
| | Count | Percentage | Count | Percentage | Count | Percentage |
| White blood cell decreased | 23 | 95.8% | 23 | 95.8% | 23 | 95.8% |
| Neutrophil count decreased | 20 | 83.3% | 19 | 79.2% | 20 | 83.3% |
| Lymphocyte count decreased | 17 | 70.8% | 12 | 50% | 17 | 70.8% |
| Anemia | 23 | 95.8% | 20 | 83.3% | 20 | 83.3% |
| Constipation | 13 | 54.2% | | | | |
| Thrombocytopenia | 22 | 91.7% | 19 | 79.2% | 19 | 79.2% |
| Elevated LDH | 10 | 41.7% | 8 | 33.3% | 1 | 4.2% |
| APTT prolonged | 7 | 29.20% | 1 | 4.2% | 1 | 4.20% |
| Hypofibrinogenemia | 7 | 29.2% | | | 1 | 4.2% |
| Bruising | 2 | 8.3% | 1 | 4.2% | | |
| Elevated ALT | 22 | 91.7% | | | 8 | 33.3% |
| Elevated AST | 18 | 75% | | | 5 | 20.8% |
| Hyperbilirubenemia | 21 | 87.5% | | | 9 | 37.5% |
| Elevated alkaline phosphatase | 20 | 83.3% | | | 1 | 4.2% |
| Pancreatitis | 3 | 12.5% | | | 3 | 12.5% |
| Thromboembolic event | 3 | 12.50% | | | 1 | 4.2% |
| Lipase increased | 1 | 4.2% | | | | |
| Nausea | 19 | 79.2% | 10 | 41.7% | 5 | 20.8% |
| Vomiting | 13 | 54.2% | 6 | 25% | | |
| Weight gain | 4 | 16.7% | | | | |
| Weight loss | 1 | 4.2% | | | | |
| Gastroesophageal reflux disease | 1 | 4.2% | | | | |
| Gastritis | 1 | 4.2% | | | | |
| Flatulence | 3 | 12.50% | 1 | 4.20% | | |
| Dysgeusia | 1 | 4.2% | | | | |
| Diarrhea | 1 | 4.2% | | | | |
| Anorexia | 6 | 25% | 2 | 8.3% | | |
| Bloating | 4 | 16.7% | 1 | 4.2% | | |
| Dehydration | 1 | 4.2% | | | 1 | 4.2% |
| Peripheral neuropathy | 18 | 75% | | | 1 | 4.20% |
| Paresthesia | 10 | 41.7% | | | | |
| Myalgia | 1 | 4.2% | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Headache | 5 | 20.8% | | | | |
| Insomnia | 6 | 25% | | | | |
| Hyperlipidemeia | 1 | 4.2% | | | 1 | 4.2% |
| Hypertriglyceridemia | 5 | 20.8% | | | 3 | 12.5% |
| Hypoalbuminemia | 16 | 66.7% | | | 2 | 8.3% |
| Hypoglycemia | 3 | 12.5% | | | | |
| Hyperglycemia | 19 | 79.2% | | | 4 | 16.7% |
| Hyponatremia | 4 | 16.7% | | | | |
| Hyperphosphatemia | 16 | 66.7% | 16 | 66.7% | | |
| Glucosuria | 1 | 4.2% | | | | |
| Adrenal insufficiency | 1 | 4.2% | | | | |
| Generalized muscle weakness | 3 | 12.5% | | | | |
| Febrile neutropenia | 3 | 12.5% | 3 | 12.5% | 3 | 12.5% |
| Fatigue | 7 | 29.2% | 6 | 25% | | |
| Sepsis | 4 | 16.7% | 2 | 8.3% | 4 | 16.7% |
| perianal abscess | 1 | 4.2% | | | | |
| Pneumonia | 2 | 8.3% | 2 | 8.3% | 2 | 8.3% |
| Fever | 2 | 8.3% | 2 | 8.3% | 2 | 8.3% |
| Enterocolitis infectious | 2 | 8.3% | | | 1 | 4.2% |
| Diastolic cardiomyopathy | 1 | 4.2% | | | | |
| Hypertension | 5 | 20.8% | | | 1 | 4.2% |
| Hypotension | 2 | 8.3% | 1 | 4.2% | 2 | 8.3% |
| Dyspnea | 2 | 8.3% | | | | |
| Edema limbs | 5 | 20.80% | | | | |
| Dry mouth | 1 | 4.2% | | | | |
| Facial edema | 1 | 4.2% | | | | |
| Sore throat | 1 | 4.2% | | | | |
| Mucositis | 3 | 12.5% | 2 | 8.40% | | |
| neck stiffness | 1 | 4.2% | | | | |
| Pain | 7 | 29.2% | 1 | 4.2% | | |
| Skin rash or changes | 2 | 8.40% | | | | |
| Proteinuria | 4 | 16.7% | | | | |
| Hiccups | 2 | 8.3% | | | | |
| Hyperhidrosis | 1 | 4.2% | | | | |
| Dizziness | 1 | 4.2% | | | | |
| Visual changes | 2 | 8.40% | 1 | 4.20% | | |

**Supplementary Figure 1. Oncoprint**. Oncoprint illustrating the frequency of pre-treatment mutations and fusions for patients with Ph-like ALL and non-Ph-like ALL.