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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Abstract

BCL-2 protein overexpression, common in B-cell acute lymphoblastic leukemia (B-ALL), including the Philadelphia chromosome (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 years (range: 18-53), 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 the 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 the Ph-like subtype (clinicaltrials.gov 05157971).

Introduction

The evolution of front-line 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 been shown to be feasibile 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 con-

veys resistance toward front-line 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 (TKI) have shown promising *in vitro* activity in selected genetic subtypes of Ph-like ALL,[9,11,12] clinical studies utilizing TKI in Ph-like ALL have demonstrated only marginal benefit,[13,14] rendering Ph-like ALL a disease with unmet therapeutic need. Despite the success with the early introduction of blinatumomab in front-line 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 other than myelosuppression, we hypothesized that the addition of a short course of venetoclax to a pediatric-type front-line regimen would be safe and would lead to improvement in MRD response for B-ALL, including the 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 I 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 (Ph-) B-ALL (clinicaltrials.gov 05157971).

Methods

Study population

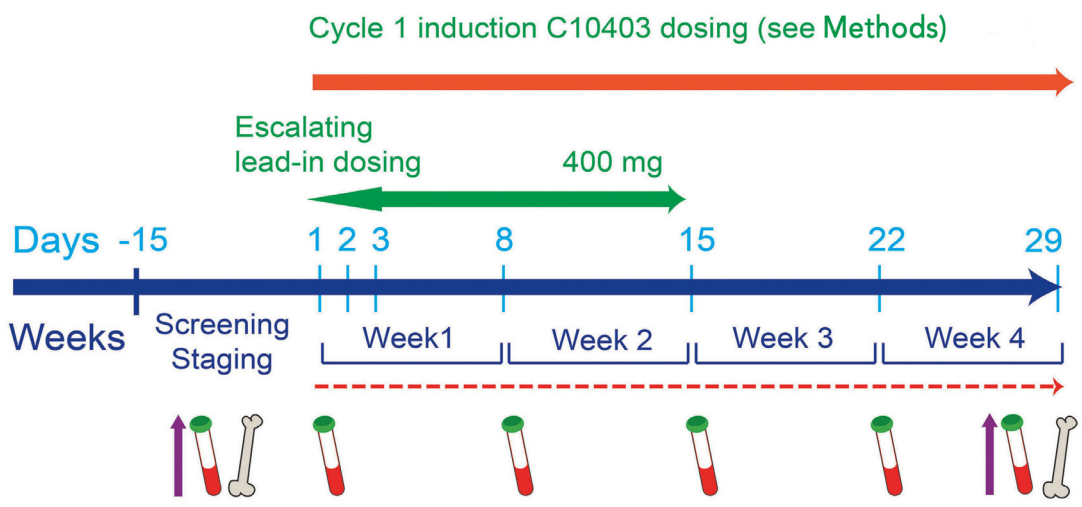
This was a prospective, single-arm, single-center phase I study with an expansion cohort investigating the safety of combining venetoclax with induction and consolidation cycles of the CALGB 10403 regimen. The study enrolled newly diagnosed adults (18-54 years) with Philadlphia-negative (Ph-) B-ALL. 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 do not 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 previously described.[22] This research was approved by the City of Hope (COH) Institutional Review Board (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 the COH. The study was designed and conducted by the investigators, who also analyzed the data.

Study design

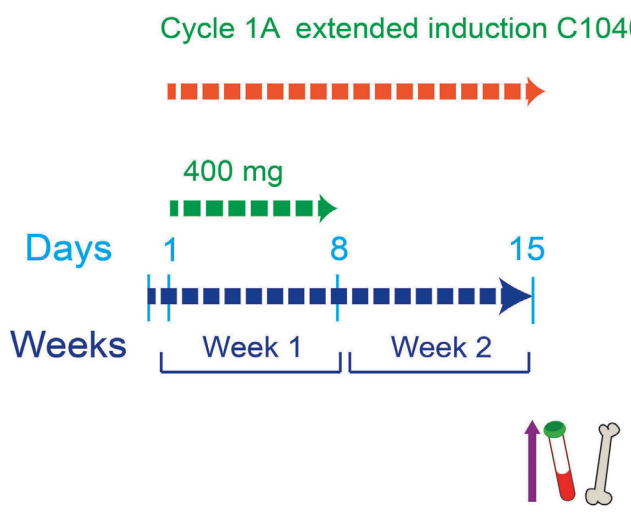
The primary objective of the study was the safety and feasibility of combining venetoclax with the CALGB 10403 regimen backbone during induction in newly diagnosed adults with Ph- B-cell ALL, and to identify the maximum tolerated dose (MTD) of venetoclax in combination with the CALGB 10403 regimen (Figure 1, *Online Supplementary Table S1*). 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 1-year overall survival (OS) and leukemia-free survival (LFS). OS is defined as 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 (100 mg day 1; 200 mg day 2; 400 mg/day days 3-14). 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 >5% residual blasts, and venetoclax was administered on days 1-7 during this cycle. We restricted venetoclax administration to only induction, extended induction if applicable, and restricted consolidation cycles to avoid cumulative prolonged cytopenia and as

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

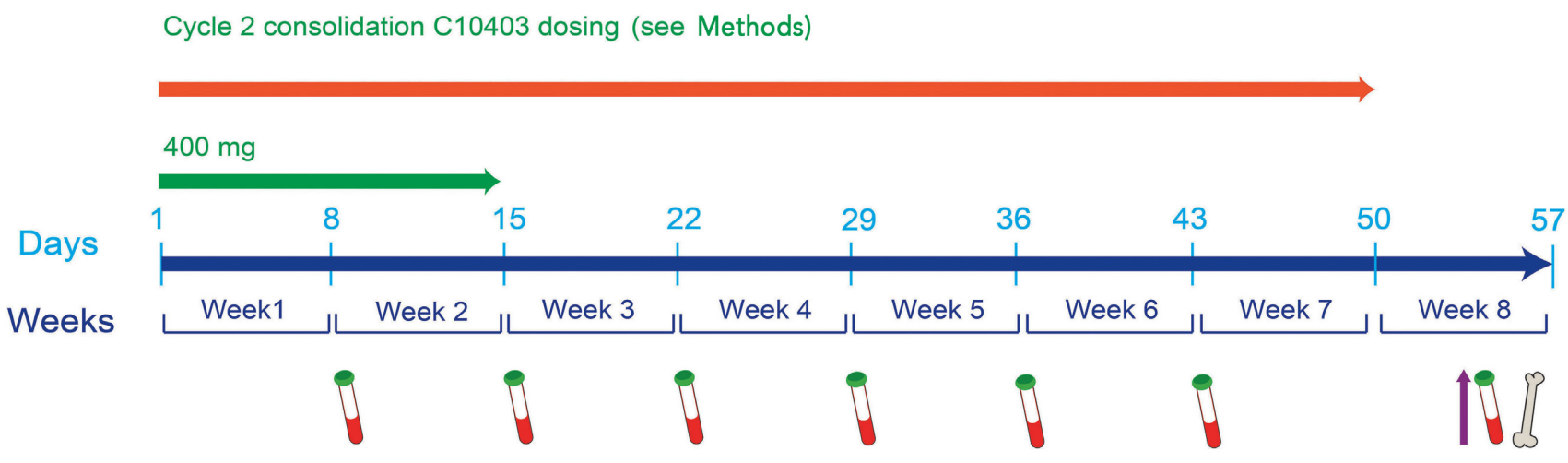


Figure 1. Study schema. PR: partial remission; SD: stable disease; CR: complete remission: Cri: CR with incomplete count recovery; CRh: CR with partial hematologic recovery.

we anticipated that the majority of Ph-like ALL patients will receive allogeneic hematopoietic stem cell transplantation (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 1,000 IU/m^2 for patients ≥40 years of age and/or patients with body mass index (BMI) ≥30. For patients who were <22 years of age, 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 at the discretion of the treating physician 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

Complete response was defined as <5% lymphoblasts in the bone marrow (BM), and the absence of circulating lymphoblasts or extramedullary disease, and absolute neutrophil count (ANC) >1x10^9/L and platelet count >100x10^9/L. CRi was defined as CR with either platelet count <100x10^9/L or/and ANC <1x10^9/L, and CRh was defined as CR with platelet count >50x10^9/L and ANC >0.5x109/L.[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.

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, USA) was performed when possible on post-induction and post-consolidation BM 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 take part in the study; 2 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. Median age was 31 years (range: 18-53), including 9 (38%) patients who were >40 years of age. 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* N=8; *P2RY8::CRLF2* N=3), and one 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 white blood cell count (WBC) at presentation in Ph-like ALL patients. Table 1 shows the study patients' characteristics. *Online Supplementary Figure S1* provides 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. The patient 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.

Median time to count recovery with neutrophil count ≥1x10^9/L and platelet count ≥100x10^9/L was 20 (range: 15-40) and 21 (range: 2-57) days from start of induction, respectively. Median time from initiating consolidation to start day 29 of consolidation was 29 days (range: 29-43), including 70% of patients who had started day 29 with no delays.

Treatment-related adverse events (TRAE) were reported in all patients. Grade ≥3 AE 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). *Online Supplementary Table S2* shows all grade TRAE attributed to either venetoclax and/or the CALGB 10403 regimen, and TRAE attributed only to venetoclax.

Table 1. Patients' characteristics.

	All patients	Ph-like	Non-Ph-like
Number of patients	24	12	12
Median age in years (range) ≥40, N (%)	31 (18-53) 9 (38)	31 (18-53) 5 (42)	31.5 (18-44) 4 (33)
Sex, N (%) Male Female	 19 (79) 5 (21)	 10 (83) 2 (17)	 9 (75) 3 (25)
Ethnicity, N (%) Hispanic Non-Hispanic	 22 (92) 2 (8)	 11 (92) 1 (8)	 11 (92) 1 (8)
Median BMI (range)	30 (19-54)	30 (22-42)	31 (19-54)
Median WBC at diagnosis, x10^9/L (range)	4 (0.19-276)	20.6 (2.9-276)	2.1 (0.19-5.6)
CNS at diagnosis, N (%) CNS-1 CNS-2	 22 (92) 2 (8)	 10 (83) 2 (17)	 12 (100) 0

Ph: Philadelphia chromosome; N: number; BMI: Body Mass Index; WBC: white blood cell count; CNS: central nervous system.

Response and outcomes

The one patient with pegasparaginase toxicity was not evaluable for response and died without disease assessment, as mentioned above. The remaining 23 (96%) patients achieved CR/CRi (CR N=21; CRi N=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 two 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 at the discretion of the treating physician. Twenty-two patients 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- 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

Table 2. Treatment-related adverse events ≥ grade 3 observed in at least 10% of patients.

Adverse event	N	%
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

N: number.

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 months (range: 1.1-24.7), 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 discussed above. Estimated 1-year OS was 96% (95% CI: 88-100%) (Figure 2A). Estimated 1-year LFS was 91% (95% CI: 80-100%) (Figure 2B).

BH3 profiling

MFC-based BH3 profiling was performed on 19 available pre-treatment BM 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 4 cases displayed resistance to treatment with BH3 peptides, and all 4 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- 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 >40 years who were otherwise ineligible for the CALGB 10403 study,[3] and half of the study population were obese, which is 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

Table 3. Efficacy outcomes and disposition.

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

N: number; Ph: Philadelphia chromosome; CR: complete remission: Cri: CR with incomplete count recovery; MRD: measurable residual disease; IGH NGS: immunoglobulin heavy next-generation sequencing; CR1: 1st CR; alloHCT: allogeneic hematopoietic cell transplantation.

regimen was associated with an outstanding MRD- CR/CRi rate by flow cytometry achieved 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 had only a low level of residual disease at 0.01%. Ph-like ALL represents a true challenge with current front-line therapy using pediatric- or adult-type regimens, and innovative front-line approaches are urgently needed. In the GIMEMA LAL1913 study, 78%, 53%, and 42% of Ph-like ALL patients were 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 DFS 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 a Ph-like signature.[3] MRD response is a highly prognostic marker and a powerful surrogate for long-term survival outcomes, surpassing most of the other prognostic 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 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 multi-agent chemotherapy. Median follow up for our patients is short, with only one pa-

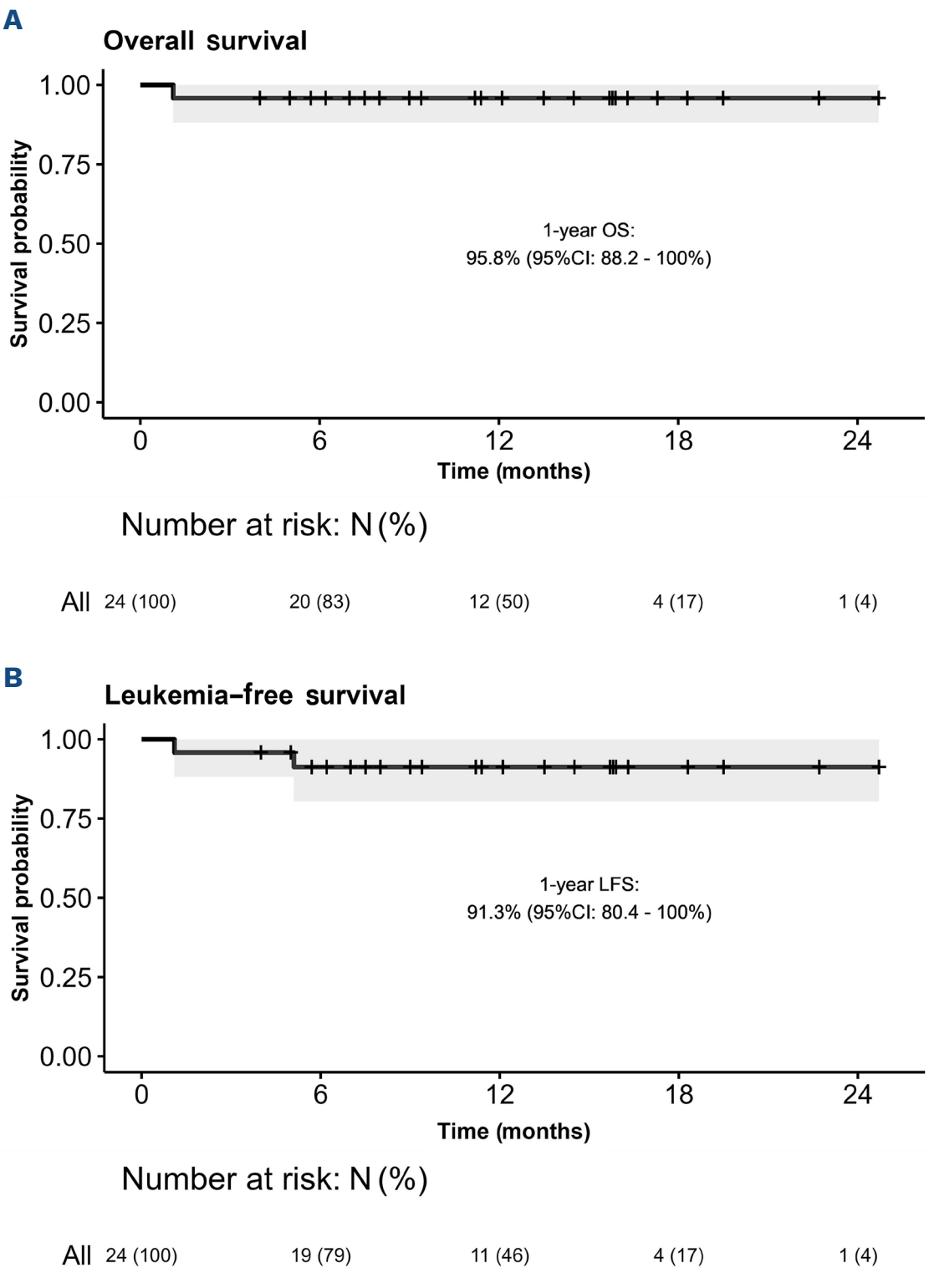


Figure 2. Survival outcomes. (A) Overall survival (OS). (B) Leukemia-free survival (LFS).

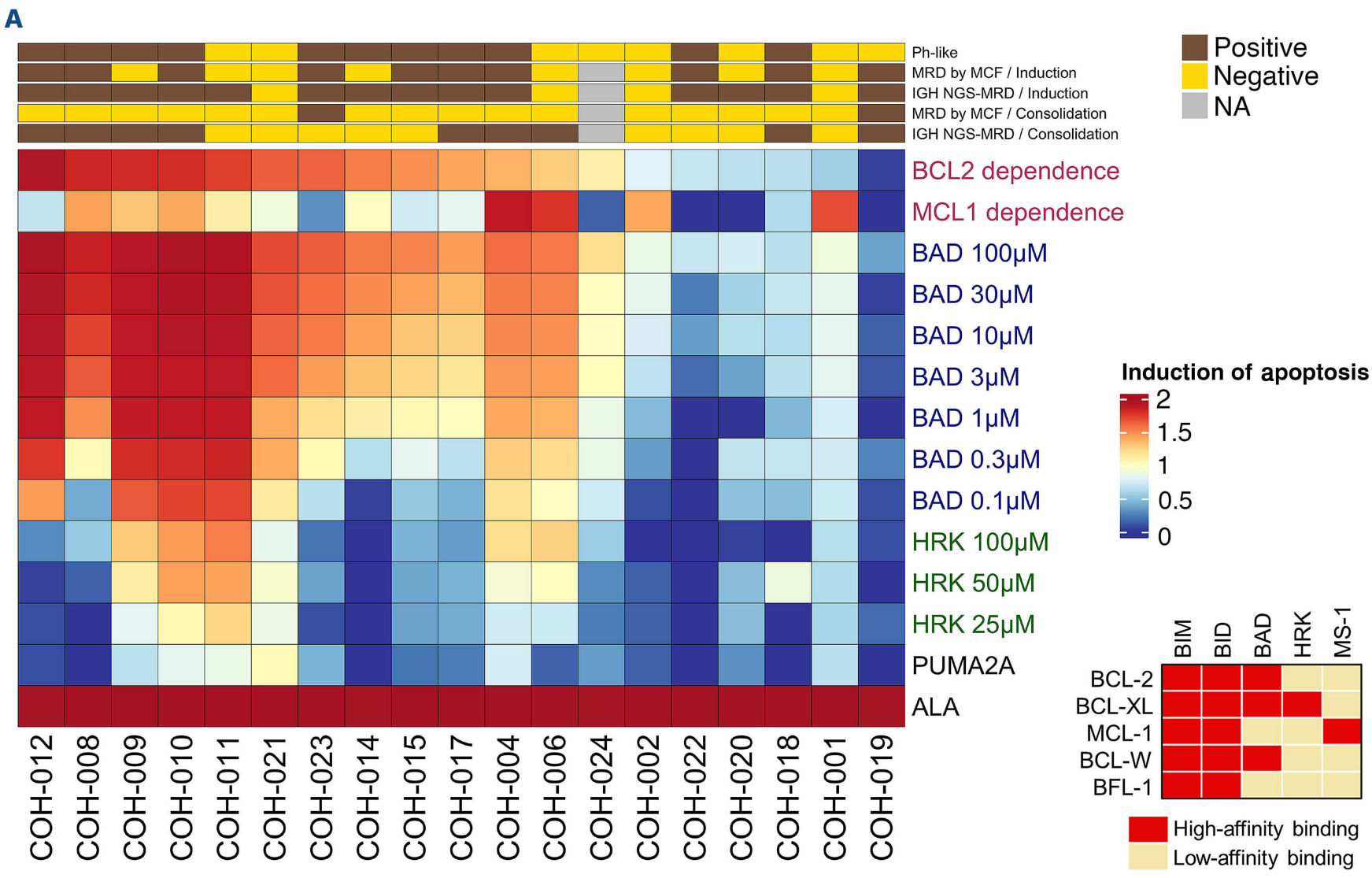


Figure 3. BH3 profiling. (A) BCL2 dependence is measured by BAD-HRK response. PUMA2A is negative control; alamethicin is positive control. (B) Correlations between BCL2 dependency and Philadelphia (Ph)-like status (top left), MCL1 dependency and Ph-like status (top right), BCL2 dependency and post-induction measurable residual disease (MRD) status by flow cytometry (bottom left), BCL2 dependency and post-induction MRD status by immunoglobulin heavy next-generation sequencing (IGH NGS) (bottom center), and BCL2 dependency and post-consolidation MRD status by IGH NGS (bottom right). MFC: multicolor flow cytometry; depol.: depolarization; NA: not available.

tient 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 DFS notwithstanding the front-line use of blinatumomab in the GIMEMA LAL2317 study.[16] Ph-like ALL is a heterogenous disease and the value of adding TKI to front-line 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 a 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 is warranted.

Disclosures

IA received research support form Abbvie and MacroGenics, and served as a consultant for Amgen, Pfizer, KiTE, Takeda, Jazz, Wugen, Syndax, and Adaptive. PK served as a consultant for Novartis, BMS, Dailchi Sankyo, Takeda, and Ascentage, and participated in the DSMB Ad Board for Treadwell. HA received research support from Incyte, and served as a consultant for Incyte, GSK, Sobi, Pharmaessentia, and Karyopharm. ASA served as a consultant for Abbvie and Astra Zeneca. MMAM received research support from NexImmune, Gilead, Miltenyi Biotec, and Incyte, and served as a consultant for Hasna Biopharma, Stemline Therapeutics, Gilead, Incyte, Tscan, TrX1, and CareDx. PSB received institutional research support from GPCR and served as a consultant for Accordant Health Services. WS served as a consultant for Jazz, Newave, Kura, and Adaptive. ASt served as a consultant for Syndax and Debio Pharma, and as a speaker bureau for Amgen. GM served as a consultant for Ostentus. VP served as consultant and a speaker bureau for Abbvie. None of the other authors have any conflicts of interest to disclose.

Contributions

IA and VP are responsible for the study concept. IA, VP, MR and JZ are responsible for study design, conduct, and supervision. IA, VA, AA, AK, HP, PK, HA, AB, SO, KSa, BB, ASA, MMAM, ASa, IL, PB, SJF, ASt, GM and VP are responsible for patient recruitment, treatment, and monitoring. MA, IL, MV, JD and JZ are responsible for the collection and assembly of clinical data. LG, WS and CS carried out correlative studies and supervision. KSh carried out the study. JZ, IA and CS analyzed and interpreted the data. IA, VP, MR, JZ and CS made the first draft of the manuscript. All authors reviewed, revised, and approved the final draft of the manuscript.

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Data-sharing statement

For original data, please contact the corresponding author: ialdoss@coh.org. Deidentified individual participant data will be shared by the corresponding author on request.

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