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A Phase I-II Study of the Combination of Ruxolitinib or Dasatinib with Chemotherapy in Patients with Philadelphia Chromosome (Ph)-Like Acute Lymphoblastic Leukemia (ALL)

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1.0 INTRODUCTION

1.1 Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia (ALL) is a malignant proliferation of lymphoid cells blocked at an early stage of differentiation. Combination chemotherapy has been the cornerstone of treatment of ALL. While currently employed induction regimens in adults with ALL now routinely result in these very high CR rates of 80-90%, none of them have yet translated into the 80-85% disease-free survival rates that are routinely achieved in pediatric ALL. In adult ALL, DFS generally has been reported to be at 40-45% at 3 years and 30-35% at 5-years.[1] Thus, the major problem with the current treatment programs in adult ALL is disease relapse due to the emergence of resistant disease. Further intensification of chemotherapy has not proved to be effective.[2] The prognosis of patients with relapsed or refractory ALL or LL is extremely poor.[3,4]

ALL in first relapse: In the largest report of relapsed adult ALL patients to date, Fielding and colleagues analyzed the outcomes of adult ALL patients in first relapse who were treated on the MRC UKALLXII/ECOG E2993 trial.[5] Of the 1508 evaluable patients, 1372 (91%) achieved CR1

of whom 609 (44% of the CR1 patients) relapsed at a median of 11 months. The median OS after relapse was only 5.5 months with a 5-year OS of 7%. The rate of achievement of CR2 was not reported. Tavernier and colleagues reported outcomes of 421 ALL patients who experienced first relapse treated on the French LALA-94 trial.[6] A CR2 was achieved in 44% patients with a median OS of 6.3 months. Oriol and colleagues reported the outcomes of 263 ALL patients in first relapse treated on 4 consecutive PETHEMA trials.[7] CR2 was achieved in 45% of patients with the median OS after relapse of 4.5 months and 5-year OS of 10%.

ALL in second relapse or greater: O'Brien and colleagues reported 18% CR rate after second salvage chemotherapy in 288 patients with ALL. The median survival of the entire cohort was only 3 months. Kantarjian and colleagues reported outcomes of patients with ALL who achieve CR2/CR3.[8] The median OS post achievement of the response was 10 months.

Overall CR rate in patients with relapsed/refractory ALL is <20% with a median survival of <6 months. In a recently reported study of clofarabine and cyclophosphamide in patients with relapsed/refractory ALL (majority were salvage 2 or greater), CR/CRp rate was 12% with a median survival of 3 months.[9] In another recently reported study in patients with relapsed/refractory ALL (salvage 2 or greater), single-agent liposomal vincristine led to CR/CRi rate of 20% with an OS of only 4.6 months.[10] Novel therapeutic strategies are clearly needed.

1.2 Ph-Like ALL

There has been significant advancement in our understanding of the biology of ALL in the last few years which provides an opportunity for 'targeted therapy'.[11,12] In 2009, a subgroup of childhood B-cell ALL patients was identified that had a gene expression signature similar to that of BCR-ABL1 (Philadelphia chromosome) positive ALL, but these patients had no Philadelphia chromosome.[13,14] These patients had frequent deletion of transcription factor *IKZF1* (also common in BCR-ABL1 positive ALL), and poor outcome.[13-15] These cases categorized as "Ph-like ALL" comprise up to 15% of childhood B-ALL[16], 20-25% in adolescents and young adults, and a higher frequency of ALL in adults (up to 30%).[17] Patients with Ph-like ALL have a very high rate of disease relapse and poor overall survival.[17-20]

In a study by the German and Dutch groups, 190 children with newly-diagnosed ALL (154 B-cell ALL, 36 T-cell ALL) were evaluated for gene expression using Affymetrix chip assay. Hierarchal clustering with 110 gene probe set clustered major subtype of B-cell pediatric ALL separated into distinct groups (*ETV6-RUNX1* (*TEL-AML1*, t(12;21) (p13.1;q22)); hyperdiploid (>50 chromosomes); *TCF3* (*E2A*)-rearranged such as *TCF3–PBX1* (t(1;19)(q23;p13)); *MLL*-rearranged; *BCR-ABL1*). There were 44 patients which did not fit into anyone of the known genetic subgroups and were classified as B-other. Of these 44 patients, 30 patients (19% of the entire B-cell ALL cohort (30/154); 68% of B-other (30/44)) had gene expression profile similar to BCR-ABL1 positive ALL. These patients are referred to as Ph-like ALL and their outcome is very poor (5-year DFS 59% vs. 84% for B-cell ALL (excluding Ph-Like ALL), p=0.01). Patients with Ph-like ALL were noted to have significantly higher WBC count than the other B-cell ALL.

Up to half of Ph-like ALL cases harbor rearrangement of *CRLF2* located at the pseudoautosomal region of Xp22.3/Yp11.3, either as a translocation to the immunoglobulin heavy chain enhancer region at 14q32.33 (*IGH-CRLF2*), or a focal deletion proximal to *CRLF2* resulting in the expression of a *P2RY8-CRLF2* fusion transcript.[18,21-25]

1.3 CRLF2 rearrangements and JAK mutations in B-cell ALL

CRLF2 encodes cytokine receptor–like factor 2 (also known as thymic stromal lymphopoietin (TSLP) receptor), a lymphoid signaling receptor molecule that forms a heterodimeric complex with interleukin-7 receptor alpha (IL7R) and binds TSLP. IL7-TSLP receptor signaling pathway is important in lymphoid development. These 2 cytokine receptors are dimeric, share IL7R, and use IL2RG (interleukin-2 receptor gamma, which is a common gamma chain shared by the receptors of various cytokines, including interleukin 2, 4, 7, 9, and 15) and CRLF2, respectively, to form heterodimers. TSLP-CRLF2 signaling has important roles in T-cell and dendritic cell development, inflammation and allergic disease and promotes B-lymphoid proliferation.[26] TSLP is produced by epithelial cells at sites of inflammation, where it activates myeloid dendritic cells and Th2 immune responses. Signaling from the TSLP receptor activates signal transducer and activator of transcription (STAT5) by phosphorylation of JAK1 and JAK2 through association with IL-7R and CRLF2, respectively.[22,27,28]

Mulligan and colleagues had identified deletion involving the pseudoautosomal region 1 (PAR1) of Xp22.3/Yp11.3 in B-cell ALL, including in several children with Down syndrome–associated ALL (DS-ALL).[15,21,29] Further analysis showed that PAR1 deletion extended from immediately upstream of *CRLF2* exon 1 to *P2RY8* intron 1 creating a fusion transcript *P2RY8-CRLF2*.[21] The breakpoints were identical in all patients and detectable by RT-PCR. These patients also had increased cell surface expression of *CRLF2*, detectable by flow-cytometry. Overall 53% (40/75) of patients with DS-ALL had *P2RY8-CRLF2* fusion. *IGH@-CRLF2* translocations, that also lead to increased CRLF2 expression, are rare in DS-ALL (only 1/75 patients in this study).[21] Importantly, *P2RY8-CRLF2* fusion was associated with *JAK2* mutations (32% vs. 4% without the fusion), most commonly at *JAK2* pseudokinase domain, *JAK2*R683. In contrast to myeloproliferative diseases, in which homozygous alteration of *JAK2*V617F is common, the JAK alterations in B-cell ALL are usually heterozygous and do not occur at *JAK2*V617.[30-34] Coexpression of *P2RY8-CRLF2* and *JAK* mutation led to constitutive JAK-STAT activation and cytokine-independent growth in Ba/F3-IL7R cells. Moreover, this transformation was attenuated by pharmacological JAK inhibition and knockdown of CRLF2 by shRNA.[21]

Russell and colleagues evaluated 97 patients, mostly children (median age 5.5 years; range, 1-76) with CRLF2 deregulation (deletion or translocations), including 41 patients with DS-ALL. [22] Overall the incidence of CRLF2 deregulation in childhood ALL was reported as 5% (4.2% deletion, 0.8% translocations). Apart from intrachromosomal amplification of chromosome 21

(iAMP21) seen in the non-DS ALL patients with CRLF2 deletion, none of the patients in this study showed established chromosomal abnormalities of prognostic significance (such as high hyperdiploidy, rearrangements of *MLL*, *BCR-ABL1*, and *ETV6-RUNX1* fusions). Quantitative real-time PCR showed an increase in CRLF2 mRNA expression in samples from patients with the CRLF2 translocations and deletion. mRNA levels were increased from 80- to >1500-fold in the translocation patients and from 5- to 100-fold in the deletion patients. Notably, mRNA levels of IL7RA and IL2RG (IL7RA and IL2RG form the heterodimeric receptor for IL-7) were normally expressed. *CRLF2* mutation screening revealed single nucleotide polymorphisms (SNPs) but no somatic mutations.[22]

Harvey and colleagues evaluated 207 children with 'high-risk' B-cell ALL enrolled on COG P9906 study with augmented BFM regimen.[18] Twenty-nine patients (14%) had CRLF2 overexpression (2/3 were *IGH@-CRLF2* translocations; 1/3 were *P2RY8-CRLF2*). Notably, there is higher rate (14%) of CRLF2 overexpression in this cohort of high-risk ALL patients, compared to 5% in unselected childhood B-cell ALL cases.[22] Also, in this 'high-risk' cohort, the *IGH@-CRLF2* translocations were more common than *P2RY8-CRLF2* fusion (2:1 incidence ratio). This is in contrast to other reports *P2RY8-CRLF2* fusion is more common than *IGH@-CRLF2* translocations (~2:1 in unselected childhood B-cell ALL and >9:1 in DS-ALL cases with CRLF2 rearrangement).[21,22] In the report by Harvey and colleagues, patients with Hispanic ethnicity were more like to have CRLF2 overexpression (35% vs. 7% in others, p <0.001).[18] *IKZF1* alternations were more common in patients with CRLF2 overexpression (81% vs. 22% in non-CRLF2 overexpressed cases, p <0.001). *JAK* mutations were more common in patients with CRLF2 overexpression (69% vs. 1% in non-CRLF2 overexpressed cases, p <0.001). Conversely, 90% of JAK mutated cases had CRLF2 rearrangements. Patients with CRLF2 deregulation had a significantly inferior 4-year RFS (35.3% vs. 71.3% for those with intact CRLF2, p=0.001). There was no difference in the outcome according to the type of CRLF2 rearrangement (translocation vs deletion). Approximately 62% of patients with CRLF2 deregulation had the Ph-Like GEP. Notably, 4/8 patients that were CRLF2-rearranged but lacked JAK mutations had a Ph–like signature suggesting the presence of additional unidentified mutations resulting in activated kinase signaling (all 4 had IKZF1 alteration). Conversely, 3/18 CRLF2-rearranged cases with JAK mutations lacked a Ph–Like GEP (all 3 had less common JAK2 or JAK1 mutations).

Yoda and colleagues reported CRLF2 overexpression in 5.9% (15/254) of adults with B-cell ALL.[25] As reported in the pediatric series, CRLF2 expression is restricted to B-cell ALL patients without known recurrent chromosomal aberrations (12.5% (15/120) in those with lacking recurring chromosomal aberrations; none in 134 patients with recurrent chromosomal aberrations). They also reported a point mutation in the CRLF2 (CRLF2 F232C, CRLF2 711 T>G) in 3 of the 14 (21%) patients with CRLF2 overexpression. CRLF2 F232C, a gain of function mutation, leads to constitutive dimerization through the cysteine residues and thereby, signal transduction. They also report that CRLF2 F232C mutation was mutually exclusive with JAK mutations, suggesting that

these mutations function within the same pathway. In this series, all patients with JAK mutations overexpressed CRLF2. They also screened patients with CLL and T-cell ALL, none of whom had CRLF2 overexpression.

Chen and colleagues evaluated a large cohort of pediatric ALL (n=1061), enrolled on the COG trials (P9905 and P9906).[35] This cohort included 562 ALL patients classified as NCI SR (with ages ranging from 1 to 9.99 years and initial WBC <50K/uL) and 499 patients classified as NCI HR (age ≥ 10 years or initial WBC ≥50K/uL). A total of 186 of the 1061 patients (17.5%) were noted to have CRLF2 overexpression (CRLF2 mRNA was assessed by quantitative RT-PCR). CRLF2 overexpression was noted in 19% of the HR cohort and 16.2% of the SR cohort. The 186 ALL patients with high CRLF2 mRNA expression had higher rates of end induction MRD (30% vs 21.3%, P = .016) and higher rates of relapse (38.2% vs 22.1%, P <.001). Patients with high CRLF2 mRNA expression also contained all of the CRLF2 genomic lesions (IGH@-CRLF2, P2RY8-CRLF2, and CRLF2 F232C), virtually all of the JAK mutations (37 of 39), and a higher frequency of IKZF1 deletions and mutations (43.3% vs 18.9%, P <.001). In addition, consistent with reports by other groups, high CRLF2-expressing ALL cases lacked common ALL-associated sentinel cytogenetic lesions. One surprising finding in this study was that only 53% of the cases with CRLF2 overexpression (9% of the entire ALL cohort) had genomic rearrangements of CRLF2 (ratio of P2RY8-CRLF2:IGH@-CRLF2 = 2.1:1). Notably, the ratio of P2RY8-CRLF2 to IGH@-CRLF2 was 1.1:1 for HR and 4.5:1 for SR cohorts. Three patients with CRLF2 overexpression (2.2% of the CRLF2 overexpressors) had CRLF2 F232C mutation. Notably, all 3 had concomitant CRLF2 aberrations (either IGH@-CRLF2 or P2RY8-CRLF2) and consistent with the report by Yoda and colleagues,[25] CRLF2 F232C mutations were mutually exclusive with JAK mutations, indicating that these mutations function within the same pathway. In this report, JAK mutations were seen in almost exclusively in patients with CRLF2 rearrangements (38% of patients with CRLF2 rearrangements had JAK mutations; 4.4% of the entire B-cell ALL cohort had JAK mutations). Of the 39 mutations in JAK, 33 were in JAK2, 6 JAK1 and 1 in JAK3. In a multivariate model for RFS in the entire cohort, only 4 variables (NCI risk status, MRD, high CRLF2 expression, and IKZF1 deletions/mutations) retained independent prognostic significance. In a multivariate model for RFS for the HR cohort, only 2 variables (MRD and high CRLF2 expression (irrespective of presence or absence of a known genomic lesion)) retained independent prognostic significance.

In the UKALLXII/ECOG2993 trial, 454 patients (15-60 year old) with available samples were evaluated for CRLF2 deregulation by FISH.[36] Incidence of CRLF2 deregulation was 5% (2/3 were *IGH@-CRLF2* translocations; 1/3 were *P2RY8-CRLF2*). In most cases, CRLF2 deregulation was not associated with other primary chromosomal abnormalities. Patients with CRLF2 deregulation had a higher WBC count, worse 5-year relapse-free survival (RFS) (30% vs. 55% for all patients, p=0.02) and worse 5-year OS (21% vs. 43% for all patients, p=0.03).

1.4 IL7R mutations in B-cell ALL

IL7R is required for normal lymphoid development. Loss-of-function mutations in *IL7R* cause autosomal recessive severe combined immune deficiency by the complete absence of T lymphocytes and the presence of B and NK cells.[37] IL-7R heterodimerizes either with IL2RG to form a receptor to IL-7, or with CRLF2 to form a receptor for TSLP. Shochat and colleagues reported gain-of-function mutations in *IL7R* in 6% (8/133) of childhood B-ALL patients overexpressing CRLF2 compared to 0.6% (1/153) in the rest of B-cell ALL group.[38] Two types of mutations in IL7R were identified. Replacement of serine with cysteine at position 185 at the extracellular domain in four patients and complex in-frame insertions and deletions resulted in the addition of 3–7 amino acids at the transmembrane domain in 5 patients. Whereas the inserted amino acids varied from patient to patient, cysteine was always included. They also showed that the presence of cysteine was critical for the gain-of-function phenotype. Biochemical and functional assays revealed that these *IL7R* mutations were activating mutations conferring cytokine-independent growth of progenitor lymphoid cells. All mutations were heterozygous and somatic. A concomitant *JAK2* mutation was present in 3/8 samples.

In contrast, Chen and colleagues reported *IL7R* mutations in 1.5% (5/335) patients with childhood B-ALL.[35] Surprisingly, only 1 of the 5 mutations was in the CRLF2 overexpression cohort giving a low frequency of 0.7% (1/141) for IL7R mutations in the CRLF2 overexpression cohort. Interestingly, *IL7R* mutations have also been reported in approximately 10% (30/295) of childhood T-ALL.[38]

1.5 JAK inhibition in B-cell ALL

CRLF2 rearrangements and JAK mutations result in activation of JAK-STAT signaling that may be amenable to therapy with JAK inhibitors such as ruxolitinib.[39] Maude and colleagues investigated the efficacy of the JAK inhibitor ruxolitinib in xenograft models of 8 pediatric B-ALL cases with and without CRLF2 and JAK mutations.[39] Ruxolitinib treatment yielded significantly lower peripheral blast counts compared with vehicle ($P < .05$) in 6 of 8 human leukemia xenografts and lower splenic blast counts ($P < .05$) in 8 of 8 samples. Enhanced responses to ruxolitinib were observed in samples harboring JAK-activating lesions and higher levels of STAT5 phosphorylation.

1.6 Activating cytokine receptor and tyrosine kinase signaling in B-cell ALL

Transcriptome and whole genome sequencing of 15 Ph-like ALL cases, 12 of which lacked CRLF2 rearrangement, identified a set of genetic alterations activating cytokine receptor and tyrosine signaling.[23] These were most commonly rearrangements resulting in chimeric fusion genes deregulating tyrosine kinases (*NUP214-ABL1*, *ETV6-ABL1, RANBP2-ABL1, RCSD1-ABL1, BCR-JAK2, PAX5-JAK2, STRN3-JAK2* and *EBF1-PDGFRB*) and cytokine receptors (*IGH-EPOR*). Up to 20% of Ph-like cases lack a chimeric fusion on mRNA-seq analysis, and sequence mutations (e.g. activating mutations of *FLT3* and *IL7R*) and structural alterations (e.g. focal deletions of

SH2B3, also known as LNK, which suppresses JAK signaling)[40] activating signaling have been identified in fusion-negative cases.[38,41] These diverse genetic alterations activate specific signaling pathways, notably *ABL1* and *PDGFRB* (both of which may be inhibited with the tyrosine kinase inhibitors (TKI) such as dasatinib) and JAK-STAT signaling (via *JAK* mutations and *JAK* fusions such as *BCR-JAK2, PAX5-JAK2, STRN3-JAK* which may be inhibited by *JAK* inhibitor such as ruxolitinib).[23,39] These rearrangements have been shown to activate signaling pathways in preclinical cell lines and xenograft models, and xenografts of Ph-like ALL are highly sensitive to TKIs *in vivo.*[23,39] Recent reports of patients with refractory *EBF1-PDGFRB* positive ALL that was exquisitely sensitive to imatinib, and *RCSD1-ABL1* positive ALL that was sensitive to dasatinib emphasizes the potential clinical utility of TKI therapy in Ph-like ALL.[42-46]

1.7 Ruxolitinib in myeloproliferative neoplasms and other hematologic malignancies

Ruxolitinib is approved by for the treatment of intermediate and high risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. Verstovsek and colleagues reported phase 1-2 study of ruxolitinib in patients with primary myelofibrosis, post−essential thrombocythemia myelofibrosis, or post−polycythemia vera myelofibrosis.[47] A dose of 25mg orally twice daily was recommended for further study. Subsequent phase III studies have used ruxolitinib dose based on baseline platelet count. In COMFORT-I trial (a phase III placebo-controlled trial) and COMFORT-II trial (a phase III trial of ruxolitinib vs. best available therapy), ruxolitinib was given at a starting dose of 20mg orally BID (if platelet count >200K/uL) or 15mg orally BID (if platelet count 100-200 K/uL).[48,49] In patients with myelofibrosis, ruxolitinib significantly improves constitutional symptoms and decreases spleen size. Ruxolitinib is myelosuppressive. In phase III studies (COMFORT 1 and 2), the rates of grade 3-4 thrombocytopenia, neutropenia, and anemia ranged from 8-13%, 7%, 42-45%, respectively.[48,49]

1.8 Dasatinib in Ph+ ALL

Dasatinib, a second tyrosine kinase inhibitor, is approved for use in patients with Ph+ ALL with resistance or intolerance to prior therapy. MD Anderson group was the first report on the combination of dasatinib with chemotherapy (Hyper-CVAD) in patients with Ph+ ALL.[50] In the front line setting, 94% patients achieved CR. Estimated 2-year survival was 64%. Grade 3-4 pleural effusion was seen in 3% of the patients. The combination of chemotherapy and dasatinib did not result in unacceptable myelosuppression, with the median time to platelet and neutrophil recovery for the induction course being 23 and 18 days, respectively. In the relapsed setting, Hyper-CVAD + dasatinib led to 89% CR/CRp rate; however, the 3-year OS was only 26%.[51]

1.9 Chemotherapy regimen (Hyper-CVAD) in B-cell ALL

We plan to use combination chemotherapy with Hyper-CVAD plus rituximab (rituximab for patients with ALL blasts expressing CD20).[52-55] We choose this regimen for the following reasons: 1) Patients with relapsed/refractory ALL can be very proliferative and therefore a

myelosuppressive chemotherapy regimen in indicated; 2) We believe that the proposed regimen can be safely combined with ruxolitinib without excess myelosuppression; 3) Leukemic cells from patients with Ph-like ALL have been shown to retain in vitro sensitivity to vincristine and steroids (these cells are more resistant to other standard ALL chemotherapy agents such as L-asparaginase and daunorubicin).[13] In addition, there is extensive clinical experience with the use of tyrosine kinase inhibitors such as dasatinib with chemotherapy in Ph(+) ALL, and we have used ruxolitinib in AML patients with no excess toxicities.[50,56]

1.10 Molecular Diagnostic Plan

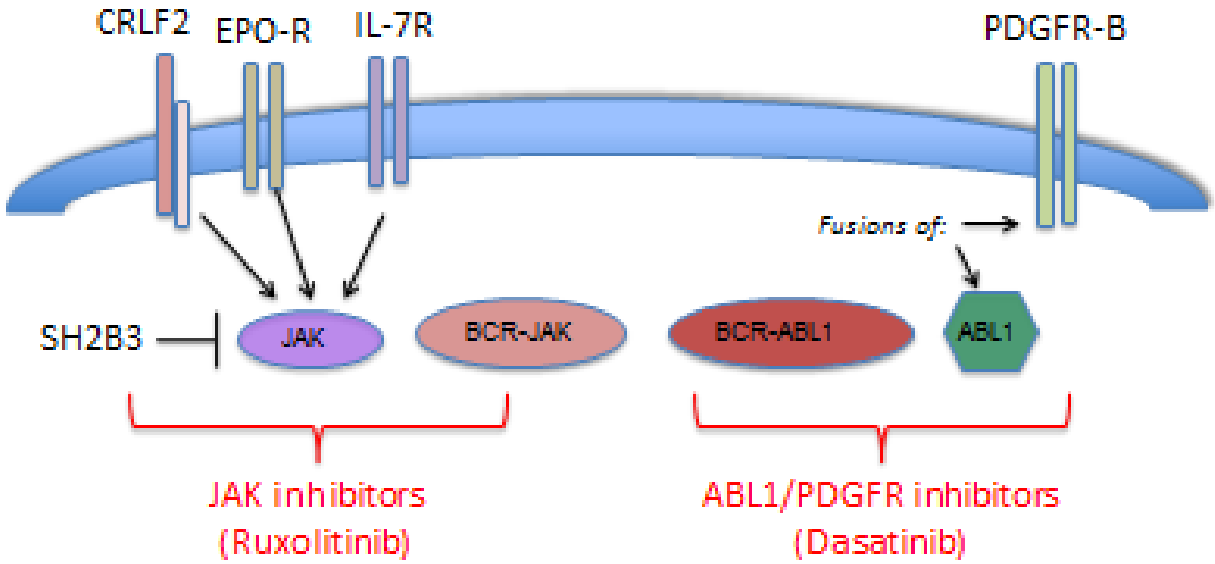
Patients will undergo flow-cytometry for CRLF2 at the CLIA-Certified flow-cytometry laboratory at MDACC. The patients will undergo molecular testing at the CLIA-Certified Clinical Molecular Diagnostic Laboratory (MDL) at the MD Anderson Cancer Center. The multiplex diagnostic assay involves mutations, translocations and copy number (amplification/ deletion) analysis of multiple genes using a next generation sequencing (NGS) platform. Briefly, total nucleic acid (DNA+RNA) will be extracted from bone marrow aspirates and analyzed using an ALL-specific NGS panel for mutations (*JAK1/2/3, FLT3, NRAS, TP53, BRAF, IL7R, NOTCH1*), translocations (*ABL1/2, PDGFRB, EPOR, JAK2, CSF1R, CRLF2, MLL, RUNX1, PBX1*) and gene deletions (*LNK, IKZF1/2/3, TP53*). The testing will be performed as a part of diagnostic clinical workup and, will be reviewed and reported by the pathologist in the patient's electronic medical record.
Alternatively, the molecular testing can be performed as a send-out test to the Nationwide Children's Hospital (CHILDLAB®, 700 Children's Drive, Columbus, OH 43205). This will involve targeted *JAK1/JAK2* mutation analysis (exons 13, 14, 15, 18, and 19 of *JAK1*; exons 16, 20 and 21 of *JAK2*) and a multiplex RT-PCR fusion detection (*ABL1* fusions, *ABL2* fusions, *PDGFRB* fusions, *CSF1R* fusions, *JAK2* fusions, *NTRK3* fusions, *TYK2* fusions).

Patients will be divided into 2 cohorts based on sensitivity of the molecular aberrations – A) Ruxolitinib arm (patients with *JAK* mutations/fusions; B) Dasatinib arm (rearrangements of *PDGFRB* and *ABL1/2*). Table 1 provides a partial list of known molecular abnormalities reported in patients with Ph-like ALL and their sensitivity to ruxolitinib or dasatinib. Figure 1 shows the various lesions in patients with Ph-like ALL and sensitivity to TKIs.

Table 1. Partial list of known molecular abnormalities reported in patients with Ph-like ALL and their sensitivity to ruxolitinib or dasatinib.

Drug Cohort	Molecular Aberrations
Ruxolitinib	CRLF2 overexpression *JAK* (*JAK1*, *JAK2*, *JAK3*) mutations *BCR-JAK2* fusion *PAX5-JAK2* fusion *STRN3-JAK2* fusion *IGH-EPOR* fusion *IL7R* mutation *SH2B3* deletion
Dasatinib	*EBF1-PDGFRB* fusion (Interstitial deletion at 5q33) *NUP214-ABL1* fusion *ETV6-ABL1* fusion (t(9;12)(q34;p13)) *RANBP2-ABL1* fusion *RCSD1-ABL1* fusion (t(1;9)(q24;q34))

Figure 1. Various lesions in patients with Ph-like ALL and sensitivity to TKIs (D. Fruman, unpublished).



2.0 OBJECTIVES

2.1 Primary Objectives

Phase I (Ruxolitinib Cohort only)

1. To determine the safety and maximal tolerated dose (MTD) of ruxolitinib in combination with chemotherapy in patients with Ph-like ALL

Phase II

1. To determine the response rate (CR/CRi) of ruxolitinib or dasatinib in combination with chemotherapy in patients with Ph-like ALL

2.2 Secondary Objectives

Phase I (Ruxolitinib Cohort only)

1. To determine the response rate (CR/CRi) of ruxolitinib in combination with chemotherapy in patients with Ph-like ALL
2. To determine the duration of response, disease-free survival and overall survival of ruxolitinib in combination with chemotherapy in patients with Ph-like ALL

Phase II

1. To determine the safety and toxicity profile of ruxolitinib or dasatinib in combination with chemotherapy in patients with Ph-like ALL
2. To determine the duration of response, disease-free survival and overall survival of ruxolitinib or dasatinib in combination with chemotherapy in patients with Ph-like ALL

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

1. Patients with previously treated B-cell ALL (relapsed and/or refractory after prior therapy)
2. Bone marrow involvement with ≥5% lymphoblasts
3. Age ≥10 years
4. Documented genetic lesion(s) known to confer susceptibility to inhibition by either ruxolitinib or dasatinib (See Table 1); or CRLF2 positivity by flow cytometry (for the Ruxolitinib cohort)
5. ECOG performance status ≤2
6. Adequate organ function (total bilirubin < 2.0 mg/dL, SGPT or SGOT < 3 x upper limit of normal [ULN], creatinine < 2 mg/dL)
7. 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 an effective contraception method during the study and for 30 days following the last dose of study drug. Females of non- childbearing potential are those who are

postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Appropriate methods of birth control include the following:

1. Any 2 of the following methods used together:
   - Birth control implants, injections, or pills (except for progesterone only pills)
   - Intrauterine device (IUD)
   - Vasectomy
   - Tubal Ligation
   - Barrier method (female or male condom with spermicide, cervical cap with spermicide, diaphragm with spermicide)
2. Male condom with spermicide and diaphragm
3. Male condom with spermicide and cervical cap

Unacceptable methods of birth control include using no birth control, withdrawal, rhythm method, vaginal sponge, any barrier method that does not use spermicide, progesterone only pills, and using male and female condoms at the same time.

8. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 30 days following the last dose of study drug
9. Patients or their legally authorized representative must provide written informed consent

3.2 Exclusion Criteria

1. Burkitt's Leukemia or Lymphoma, T-cell ALL or lymphoblastic lymphoma
2. Patients having undergone prior allogeneic stem cell transplant within 3 months or having active graft versus host disease
3. Patient is pregnant or breastfeeding
4. Patients with uncontrolled active infections (Fever ≥38°C, Septic shock)
5. Isolated extramedullary relapse (i.e. testicular, central nervous system)
6. Current or chronic hepatitis B or C infection, or known seropositivity for HIV
7. Concurrent chemotherapy (except intrathecal chemotherapy)
8. Major surgery within 4 weeks prior to first study dose
9. Systemic chemotherapy/radiotherapy/investigational therapy within 14 days (with the exception of hydroxyurea and steroids) prior to starting therapy. For patients receiving ALL maintenance with 6-mercaptopurine, methotrexate, vincristine, and steroids - these agents should be discontinued at least 48 hours prior to start of study drugs. For patients on oral targeted therapies (such as imatinib, dasatinib, ponatinib), - these agents should be discontinued at least 48 hours prior to start of study drugs.
10. Patients must have recovered from acute non hematologic toxicity (to ≤ grade 1) of all previous therapy prior to enrollment
11. Known active central nervous system (CNS) leukemia, as defined by unequivocal morphologic evidence of lymphoblasts in the cerebrospinal fluid (CSF), use of CNS-directed local treatment for active disease within the prior 28 days, symptomatic CNS leukemia (i.e., cranial nerve palsies or other significant neurologic dysfunction) within 28 days. Patients may have history of CNS leukemic involvement if definitively treated with prior therapy and no evidence of

active disease (defined as ≥2 consecutive spinal fluid assessments with no evidence of disease) at the time of registration. Prophylactic intrathecal chemotherapy is not a criterion for exclusion.

12. Patients with active heart disease (NYHA class 3-4 as assessed by history and physical examination, unstable angina/stroke/myocardial infarction within the last 6 months)
13. Patients with a cardiac ejection fraction (as measured by either MUGA or echocardiogram) <40% (Note: Patients who have had prior anthracycline exposure of >250 mg/m^2 may be eligible after discussion with the PI)
14. Second malignancy other than basal cell or squamous cell carcinoma of the skin or in situ carcinoma of the cervix or the breast, unless they are successfully treated with curative intent for more than 2 years before entering the study
15. Malabsorption syndrome or other conditions that preclude enteral route of administration
16. Patients requiring strong CYP3A4 inhibitors (See Appendix 1)
17. Other severe 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.

4.0 TREATMENT PLAN

This is an open label phase I-II study of single-agent ruxolitinib or dasatinib in patients with Ph-like ALL. All patients will undergo molecular testing per Section 1.10. This will be done as part of the screening bone marrow testing (peripheral blood could be considered for this testing in place of bone marrow aspirate, if there are sufficient blasts in the peripheral blood). Based on the molecular profile, patients will be stratified into 2 cohorts- Cohort A (ruxolitinib arm); Cohort B (dasatinib arm).

For patients who fail to respond to a single agent ruxolitinib or dasatinib by 3 weeks (earlier if evidence of progressive disease), Hyper-CVAD chemotherapy will be added. Single-agent ruxolitinib or dasatinib cycle will be cycle 0. Hyper-CVAD intensive cycles will be labelled cycles 1-8. The hyper-CVAD regimen consists of an intensive phase comprised of 8 cycles of chemotherapy alternating courses of hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) with courses of high-dose methotrexate and cytarabine every 21 days (or later depending on blood count recovery from myelosuppression). Maintenance phase chemotherapy with POMP (6-mercaptopurine, vincristine, methotrexate, and prednisone) will commence after the completion of the intensive phase of chemotherapy. Ruxolitinib or dasatinib will be given continuously concurrently with the intensive and maintenance phases.

- Note: Patients with CD20 expression (≥1% expression in leukemic blasts by flow-cytometry) will receive 8 doses of rituximab (Rituximab 375 mg/m2 on days 1 and 11 (± 2 days) for cycles 1 and 3, and days 1 and 8 (± 2) days for cycles 2 and 4).

Cohort A (Ruxolitinib)

In the Phase I part, the eligible patients will receive ruxolitinib at the starting dose of 15 mg orally twice daily as per the dose schedule below.

Dose level	Ruxolitinib dose (Adults, Age ≥18 years)	Ruxolitinib dose (Pediatric Patients, Age ≥10 and <18 years)
-2	5 mg twice daily	2.9 mg/m^2 twice daily (Max. 5 mg twice daily)
-1	10 mg twice daily	5.9 mg/m^2 twice daily (Max. 10 mg twice daily)
1 (starting dose)	15 mg twice daily	8.8 mg/m^2 twice daily (Max. 15 mg twice daily)
2	20 mg twice daily	11.8 mg/m^2 twice daily (Max. 20 mg twice daily)
3	25 mg twice daily	14.7 mg/m^2 twice daily (Max. 25 mg twice daily)

Disease assessment with a bone marrow aspirate will be performed after cycle 0 (each cycle = 21 days). Patients having a response (CR, CRi, PR) can continue with ruxolitinib monotherapy. For patients that continue with monotherapy, the cycle will remain labelled as Cycle 0. For patients without a response, Hyper-CVAD chemotherapy will be added to ruxolitinib. DLT assessment will be the duration of the ruxolitinib monotherapy and the first cycle of the combination of ruxolitinib and chemotherapy. Each cycle of Hyper-CVAD chemotherapy is 21 days. Note: patients with clinically progressive disease earlier than day 21 assessment can start the Hyper-CVAD chemotherapy at an earlier time point. Steroids (up to 40mg/day of dexamethasone or equivalent for 4 days) and/or hydroxyurea are allowed for the first 2 weeks of the study period to control rapidly proliferating disease. Patients will undergo disease assessments with a bone marrow aspirate at the end of every cycle (disease assessment interval can be increased to every 2-3 cycles once the patient has achieved CR/CRi).

For pediatric patients (<18 years of age) – the starting ruxolitinib dose will be 8.8 mg/m^2 twice daily (Max. 15 mg twice daily). Please see Appendix 2 for the pediatric dosing table.

DLT is defined as clinically significant non-hematologic adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications that meets any of the following criteria:

- Non-hematological Grade 3 laboratory abnormalities lasting > 7 days OR non-hematological Grade 4 laboratory abnormalities of any duration

Note: (1) Grade 3 or 4 nausea, vomiting and diarrhea will be considered DLT only if not controlled by optimal therapy
(2) Grade 3 biochemical abnormalities (e.g., lipase or bilirubin elevation) will only be considered DLT if accompanied by clinical consequences.
(3) Grade 3 or 4 electrolyte abnormalities will only be considered DLT if possibly related to study drug and not corrected by optimal replacement therapy.

- Any other non-hematological AE of Grade ≥3

- Hematologic DLT is defined as absolute neutrophil count (ANC) <0.5 x10^9/L or platelet count <25 x10^9/L with a hypocellular bone marrow lasting for 6 weeks or more after the start of a course in the absence of residual leukemia (i.e., with less than 5% blasts). (In case of a normocellular bone marrow with <5% blasts, 8 weeks with pancytopenia will be considered DLT). Anemia will not be considered for the definition of DLT.

Cohort B (Dasatinib)

Eligible patients will receive dasatinib monotherapy at 100 mg orally once daily. This dose is lower than the FDA approved dose of 140 mg once daily for patients with Ph+ ALL. Several studies have reported safety of dasatinib 100 mg once daily dosing with chemotherapy for patients with Ph+ ALL and therefore there is no need for a Phase I part.[50] Disease assessment with a bone marrow aspirate will be performed after cycle 0 (each cycle = 21 days). Patients having a response (CR, CRi, PR) can continue with dasatinib monotherapy. For patients that continue with monotherapy, the cycle will remain labelled as Cycle 0. For patients without a response, Hyper-CVAD chemotherapy will be added to the dasatinib. Note: patients with clinically progressive disease earlier than day 21 assessment can start the Hyper-CVAD chemotherapy at an earlier time point. Steroids (up to 40mg/day of dexamethasone or equivalent for 4 days) and/or hydroxyurea are allowed for the first 2 weeks of the study period to control rapidly proliferating disease. Patients will undergo disease assessments with a bone marrow aspirate at the end of every cycle (disease assessment interval can be increased to every 2-3 cycles once the patient has achieved CR/CRi).
For pediatric patients (<18 years of age) – the dasatinib dose will be 60 mg/m2 orally once daily (Maximum dose 100 mg daily). Please see Appendix 2 for the pediatric dosing table.

5.0 TREATMENTS ADMINISTERED

5.1 Ruxolitinib

- Ruxolitinib, previously referred as INCB018424 phosphate, is a substituted pyrrolopyrimidine compound that acts as a potent and selective inhibitor of the Janus kinase family of enzymes. Ruxolitinib is a novel, potent, and selective inhibitor of the JAKs with modest selectivity for JAK2. Ruxolitinib potently (IC50 values < 5 nM) inhibits JAKs, yet it does not significantly inhibit (<30% inhibition) a broad panel of 26 other kinases when tested at 200 nM (approximately 100 times the average IC50 value for JAK enzyme inhibition). Moreover, in cell-based assays relevant to the pathogenesis of MPDs, such as JAK-STAT signaling and the growth of cytokine-dependent lines, ruxolitinib demonstrated excellent potency (IC50 values of 80-141 nM). This effect was not due to general cytotoxicity, because ruxolitinib (up to 25 μM) had no significant effect on the growth of cytokine-independent cell lines transformed by the Bcr-Abl oncogene. In addition, ruxolitinib inhibited JAK/STAT signaling and growth of a cell line expressing the JAK2 mutant variant (JAK2V617F) that has been implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPD. Additional details as to the in vitro pharmacology of ruxolitinib may be found in the Investigator's Brochure (IB) (Edition 12, Dated 11th September 2013 with safety cut-off date of 22nd July, 2013).
- The chemical name of ruxolitinib is (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1Hpyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate. Ruxolitinib has a molecular formula of C17H21N6O4P and a molecular weight of 404.36.
- Ruxolitinib drug product will be provided as 5mg or 25mg strength tablets. The tablet formulation contains the active ingredient along with commonly used excipients. All excipients are of compendia grade.
- The medication will be provided for free to participants in this study by the manufacturer, Incyte Inc.
- The 5 mg tablets are stable for six months at 40C/75% RH and at least 24 months at 25C/60% RH. The 25 mg tablets are stable for six months at 40C/75% RH and at least 36 months at 25C/60% RH. Additional details may be found in the Investigator's Brochure (IB) (Edition 12, Dated 11th September 2013 with safety cut-off date of 22nd July, 2013).
- Ruxolitinib will be administered twice daily orally, without regard to food.
- Returned or expired study drugs will be destroyed per MDACC policy.
- Prior to advancing/changing dose levels a cohort summary will be completed and submitted to the IND Medical Monitor for review and approval.
- Dose modifications – For ruxolitinib related toxicities, the following dose modifications are proposed

Dose level	**Ruxolitinib dose (Adults, Age ≥18 years)**	**Ruxolitinib dose (Pediatric Patients, Age ≥10 and <18 years)**

-2	5 mg twice daily	2.9 mg/m^2 twice daily (Max. 5 mg twice daily)
-1	10 mg twice daily	5.9 mg/m^2 twice daily (Max. 10 mg twice daily)
1 (starting dose)	15 mg twice daily	8.8 mg/m^2 twice daily (Max. 15 mg twice daily)
2	20 mg twice daily	11.8 mg/m^2 twice daily (Max. 20 mg twice daily)
3	25 mg twice daily	14.7 mg/m^2 twice daily (Max. 25 mg twice daily)

Please see Appendix 2 for the pediatric dosing table.

5.2 Dasatinib

- Dasatinib is a multityrosine kinase inhibitor with activity against BCR-ABL, the SRC family of kinases (SFKs), c-KIT, EPHA2, and platelet derived growth factor (PDGFR-β) at nanomolar concentrations.
- The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C22H26ClN7O2S • H2O, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01.
- Dasatinib is manufactured and distributed by Bristol-Myers Squibb.
- It is approved for use in newly diagnosed patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, patients with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib, and patients with Philadelphia chromosome-positive ALL.
- Commercial supply of dasatinib will be used for this study.
- Dasatinib will be administered once daily orally, without regard to food.
- Returned or expired study drugs will be destroyed per MDACC policy.
- Dose modifications – For dasatinib related toxicities, the following dose modifications are proposed

Dose level	**Dasatinib dose (Adults, Age ≥18 years)**	**Dasatinib dose (Pediatric Patients, Age ≥10 and <18 years)**
-3	20 mg once daily	11.8 mg/m2 orally once daily

		(Max. 20 mg daily)
-2	50 mg once daily	30 mg/m2 orally once daily (Max. 50 mg daily)
-1	70 mg once daily	41.2 mg/m2 orally once daily (Max. 70 mg daily)
1 (starting dose level)	100 mg once daily	60 mg/m2 orally once daily (Max. 100 mg daily)

Please see Appendix 2 for the pediatric dosing table.

5.3 Hyper-CVAD plus Rituximab regimen

- Hyper-CVAD consists of 8 cycles of dose intensive therapy with hyper-CVAD (odd courses) alternating with high-dose methotrexate and cytarabine (even courses) administered approximately every 21 days (or later to allow for recovery from myelosuppression or infection).
- Rituximab (anti-CD20 monoclonal antibody) will be administered to patients with leukemic blasts expressing CD20. Rituximab 375 mg/m2 days 1 and 11 (± 2) days for cycles 1 and 3, and days 1 and 8 (± 2) days for cycles 2 and 4.
- Anti-emetic therapy with each course of intensive chemotherapy as indicated.
- G-CSF 5 mcg/kg/day (rounded) within 72 ± 48 hours after completion of chemotherapy until neutrophil recovery 1 x 10^9/L or higher. G-CSF may be stopped earlier for bone pain or other related toxicity. Pegfilgrastim (given 6 mg subcutaneously for one dose approximately 24 hours after completion of the chemotherapy) may be substituted for G-CSF at the discretion of the treating physician.
- Prophylactic antibacterial antibiotics, antifungal agents, and antiviral agents are recommended for anti-infective prophylaxis during periods of neutropenia as per standard practice. Use of specific agents will be left to the treating physician's discretion.
- Next course may be started when granulocyte count $\geq$ 1 x 10^9/L and platelet count $\geq$ 50 x 10^9/L, following discontinuation of G-CSF for at least 24 hours. Courses may be started with dose reductions of the chemotherapy prior to full count recovery if the treatment is delayed (e.g., 28 days or later from the start of last course) and the start of next course is deemed in the best interest of the patient by the treating physician.
- Patients will be required to receive all chemotherapy treatments at MDACC. For the first two treatment courses, patients will be monitored at MDACC. Subsequently, the patients may obtain labs and be monitored by the local oncologist under directions by the treating physician at MDACC and/or study chair. To assure adequate monitoring of the study, the letter will be provided to the treating physicians. The participants must return to MDACC at least every 30 days for clinic visits and to obtain a new supply of ruxolitinib/dasatinib. PI/MDACC treating physician must review the lab results, determine clinical significance and sign and date the lab report.

- Central nervous system (CNS) management: Intrathecal and/or intra-Ommaya chemotherapy for CNS prophylaxis is permitted concurrently with the systemic chemotherapy. Suggested regimen: intrathecal methotrexate 12 mg (6 mg via Ommaya reservoir) day 2 (± 2 days) and cytarabine 100 mg day 7 (± 2 days) of each of the first 4 cycles of Hyper-CVAD chemotherapy. Total number of treatments for CNS prophylaxis should not exceed 8 (in the absence of CNS disease). Alternative regimens are permitted if deemed in the best interest of the patient according to discretion of the treating physician. If the patient develops active CNS disease while on study, the suggested CNS management is as follows: intrathecal and/or intra-Ommaya methotrexate alternating with cytarabine twice weekly until CSF clear; then once weekly for 4 weeks, then back to prophylaxis schedule. Radiotherapy for symptomatic CNS disease is allowed.

5.4 Hyper-CVAD (Courses 1, 3, 5, 7)

- Cyclophosphamide (CTX) 300 mg/m^2 IV over 3 hours every 12 hours x 6 doses days 1, 2, 3 (total dose 1800 mg/m^2).
- MESNA 600 mg/m^2/d IV continuous infusion daily for 24 hours days 1-3.
- Doxorubicin 50 mg/m^2 IV over 24 hours via central venous catheter on day 4, after last dose of CTX given (infuse over 48 hours in patients with reduced ejection fractions). May be given by shorter infusion if difficulty with central venous access.
- Vincristine 2 mg IV on day 4 (± 2) and day 11 (± 2 days). Vincristine is not myelosuppressive and will be given on day 11 while patients are receiving G-CSF; no known adverse effects have been observed with the two agents given together. For patients <18 years old, the vincristine dose will be 1.5mg/m2 with a maximum dose of 2mg.
- Dexamethasone 40 mg IV or orally daily days 1-4 (± 2 days) and days 11-14 (± 2 days). For patients <18 years old, the dexamethasone dose will be 20mg/m2 with a maximum of 40mg.
- Rituximab 375 mg/m2 days 1 and 11 (± 2) days for cycles 1 and 3.
- G-CSF 5 mcg/kg/day (rounded) within 72 ± 48 hours after completion of chemotherapy until neutrophil recovery 1 x 10^9/L or higher. G-CSF may be stopped earlier for bone pain or other related toxicity. Pegfilgrastim (given 6 mg subcutaneously for one dose approximately 24 hours after completion of the chemotherapy) may be substituted for G-CSF at the discretion of the treating physician.
- Next course may be started when granulocyte count $\geq$ 1 x 10^9/L and platelet count $\geq$ 50 x 10^9/L, following discontinuation of G-CSF for at least 24 hours. Courses may be started with dose reductions of the chemotherapy prior to full count recovery if the treatment is delayed (e.g., 28 days or later from the start of last course) and the start of next course is deemed in the best interest of the patient by the treating physician.
- CNS prophylaxis at the discretion of the treating physician. Suggested regimen: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) day 2 (± 2 days) and cytarabine 100 mg intrathecally or intra-Ommaya day 7 (± 2 days) during cycles 1 and 3.

Tumor lysis prophylaxis with allopurinol, intravenous alkalization, oral bicarbonate for course 1 as per standard practice. Urate oxidase may be substituted for allopurinol.

5.5 Hyper-CVAD (Courses 2, 4, 6, 8)

- Methotrexate (MTX) 200 mg/m^2 IV over 2 hours followed by 800 mg/m^2 IV over 22 hours day 1.
- Solumedrol 50 mg IV over 2 hours approximately every 12 hours for 6 doses days 1-3. For patients <18 years old, the solumedrol dose will be 25mg/m2 with a maximum of 50mg.
- Cytarabine 3 gm/m^2 IV over 2 hours every 12 hours for 4 doses on days 2, 3.
  - Reduce the cytarabine to 1 gm/m^2 IV over 2 hours every 12 hours for 4 doses days 2, 3 for:
    - Age $\geq$ 60 years
    - Creatinine $\geq$ 1.5 mg/dL
    - Serum MTX level > 20 μM at time "0" (see below), confirmed on repeat sample
    - Neurotoxicity (grade 2 reversible cerebellar toxicity or other cytarabine- related CNS toxicity) with prior course.
  - Reduce the cytarabine to 1 gm/m^2 IV continuous infusion days 2, 3 for:
    - Grade 2 reversible cerebellar toxicity related to ara-C 1 g/m2 or grade 3 reversible cerebellar toxicity related to any dose of ara-C.
- Leucovorin rescue 50 mg IV followed by 15 mg IV every 6 hours for 8 doses (or until MTX cleared) beginning 12 hours (± 2 hours) post MTX completion, e.g., approximately 36 hours from start of MTX. Additional rescue allowed as indicated for elevated levels or delayed MTX clearance. For patients <18 years old, leucovorin will be given at 100mg/m2 IV followed by 15mg/m2 IV every 6 hours for 8 doses (or until MTX cleared) beginning 12 hours (± 2 hours) post MTX completion.
- Check serum MTX levels around time 0 hour, 24 hours and 48 hours post completion of MTX unless cleared (e.g. 0.15 μM or less).
  - if > 20 μM at time "0", hold cytarabine and repeat level; if continues to be > 20 μM reduce cytarabine to 1 gm/m^2 IV over 2 hours every 12 hours for 4 doses on days 2, 3.
  - if > 1 μM at 24 hours or > 0.1 μM at 48 hours, increase leucovorin rescue until serum MTX level < 0.1 μM. Clearance to levels 0.15 μM or less is acceptable in patients with normal renal function.
  - Consider oral acetazolamide 250 mg orally BID to promote MTX excretion if urine pH <7.0.
- Rituximab 375 mg/m2 days 1 and 8 (± 2) days for cycles 2 and 4.
- G-CSF 5 mcg/kg/day (rounded) within 72 ± 48 hours after completion of chemotherapy until neutrophil recovery 1 x 10^9/L or higher. G-CSF may be stopped earlier for bone pain or other related toxicity. Pegfilgrastim (given 6 mg subcutaneously for one dose

approximately 24 hours after completion of the chemotherapy) may be substituted for G-CSF at the discretion of the treating physician.

- Next course may be started when granulocyte count $\geq$ 1 x 10^9/L and platelet count $\geq$ 50 x 10^9/L, following discontinuation of G-CSF for at least 24 hours. Courses may be started with dose reductions of the chemotherapy prior to full count recovery if the treatment is delayed (e.g., 28 days or later from the start of last course) and the start of next course is deemed in the best interest of the patient by the treating physician.
- CNS prophylaxis at the discretion of the treating physician. Suggested regimen: Methotrexate 12 mg intrathecally (6 mg via Ommaya reservoir) day 2 (± 2 days) and cytarabine 100 mg intrathecally or intra-Ommaya day 7 (± 2 days) during cycles 2 and 4.

5.6 Maintenance phase chemotherapy (POMP maintenance)

- Patients may be moved from the intensive chemotherapy phase to the maintenance phase prior to completion of 8 cycles of chemotherapy if significantly intolerant or at the discretion of the treating physician after discussion with the Principal Investigator.
- Maintenance chemotherapy with 6-mercaptopurine (6-MP), methotrexate (MTX), vincristine, and prednisone (POMP) for approximately 24 months beginning at level 0 (or lower dose level if previous toxicity warrants).
- A maintenance cycle will be defined as 28 days.
- 6-mercaptopurine 50 mg tablets orally 3 times daily. For patients <18 years old, the 6-mercaptopurine dose will be 75mg/m2 divided TID with a maximum dose of 150mg divided TID.
- Methotrexate 20 mg/m^2 (rounded) orally weekly
- Vincristine 2 mg IV approximately every 28 days. For patients <18 years old, the vincristine dose will be 1.5mg/m2 with a maximum dose of 2mg.
- Prednisone 200 mg P.O. daily days 1 to 5 approximately every 28 days, starting with vincristine (if given). For patients <18 years old, the prednisone dose will be 100mg/m2 with a maximum dose of 200mg.
- Note that dose adjustments of POMP (see section 5.7) are guidelines. Dose adjustments should be individualized to the patient, as differential toxicities between 6-mercaptopurine and methotrexate may be difficult to discern.
- Dose adjustments for myelosuppression include MTX and 6-MP, but not vincristine or prednisone (the latter should remain 200 mg unless steroid myopathy or other uncontrolled significant toxicity occurs). Titrate to keep granulocytes >= 1 x 10^9/L and platelet count >= 50 x 10^9/L.
- Antiviral prophylaxis for herpes zoster is strongly encouraged.
- Consider antifungal prophylaxis during days of prednisone.
- Consider PCP prophylaxis.

- After completion of POMP maintenance, patients may continue ruxolitinib or dasatinib indefinitely, as long as they are responding to the treatment and without intolerable side-effects.

5.7 Suggested dose modifications

- Dose reductions for components beyond those specified in the protocol are permitted at the discretion of the treating physician. Dose escalation beyond doses specified in the protocol is not permitted.
- Cytarabine (ara-C)
  - Reduce to 1 gm/m^2 IV over 2 hours every 12 hours for 4 doses on days 2, 3:
    - Age $\geq$ 60 years.
    - Creatinine $\geq$ 1.5 mg/dL.
    - Serum MTX level > 20 μM at time "0" (see below), confirmed on repeat sample.
    - Neurotoxicity (grade 2 reversible cerebellar toxicity or other cytarabine- related CNS toxicity) with prior course.
  - Reduce the cytarabine to 1 gm/m^2 IV continuous infusion days 2, 3 for:
    - Grade 2 reversible cerebellar toxicity related to ara-C 1 g/m2 or grade 3 reversible cerebellar toxicity related to any dose of ara-C.
- Vincristine
  - Reduce to 1 mg IV (50% reduction). For patients <18 years old, reduce vincristine dose to 0.75mg/m2 with a maximum of 1 mg.
    - Total bilirubin > 2 mg/dL and < 3 mg/dL.
    - Grade 2 persistent peripheral neuropathy.
    - Eliminate for total bilirubin $\geq$ 3 mg/dL and/or grade 3-4 neurotoxicity (including ileus and/or peripheral neuropathy).
- Doxorubicin
  - Reduce by 50% for total bilirubin 2 to $\leq$3 mg/dL
  - Reduce by 75% for total bilirubin 3.1 to $\leq$5 mg/dL.
  - Eliminate for total bilirubin level > 5 mg/dL.
  - Administer over 48 hours in patients with reduced (< 50%) ejection fractions.
- Methotrexate (intravenous)
  - Reduce by 25%-50% for grade 3 or worse mucositis with prior MTX course.
  - Reduce by 50% for calculated creatinine clearance (GFR) 10 - 50 mL/min.
  - Hold MTX if GFR < 10 mL/min.
  - Reduce by 25% to 75% for delayed excretion and/or nephrotoxicity with prior methotrexate course.
  - Reduce by 50% for pleural effusion or ascites (drain effusion if possible).
- Methotrexate (oral)
  - Decrease by one dose level for mucositis > grade 2

- Decrease by one dose level for total bilirubin > 2.5 mg/dL or elevation transaminases ≥ 5 x upper limit normal
- Hold if granulocyte count nadir < 0.5 x 10^9/L or platelet count < 10 x 10^9/L, resume with decrease in one dose level or lower depending on duration of cytopenias.

- 6-mercaptopurine
  - Decrease by one dose level for total bilirubin > 2.5 mg/dL or elevation transaminases ≥ 5 x upper limit normal
  - Hold if granulocyte count nadir < 0.5 x 10^9/L or platelet count < 10 x 10^9/L, resume with decrease in one dose level or lower depending on duration of cytopenias.
- For POMP maintenance - Dose adjustments for myelosuppression include MTX and 6-MP, but not vincristine or prednisone (the latter should remain 200 mg unless steroid myopathy or other uncontrolled significant toxicity occurs). Titrate to keep granulocytes >= 1 x 10^9/L and platelet count >= 50 x 10^9/L.
- Suggested POMP maintenance dose levels:

Dose Level	MTX (mg/m^2) (Rounded)	6-MP (mg/d)	VCR (mg)	Prednisone (mg)
0	20	150	2	200
-1	15	100	1	100
-2	10	50	0	50
-3	5	50	0	0

- Dosing modifications based on age and performance status will be permitted on cycles 1-8 and maintenance intensifications. Suggested dose adjustments as below:

	<60 years	60-74 years and PS 0-2	>74 years; ≥60 years and PS 3-4
Cyclophosphamide (mg/m^2)	300	250	200
Doxorubicin (mg/m^2)	50	37.5	25
Vincristine (mg)	2	2	1
Dexamethasone (mg)	40	20	20
Methotrexate (mg/m^2)	200/800	100/400	50/100
Cytarabine (g/m^2)	3	1	0.5

NOTE: Age 60 – 64 with PS 0-1 may be treated with full doses (except for reduction of cytarabine to 1 g/m2) at the discretion of the treating physician

6.0 DOSE MODIFICATIONS FOR TOXICITIES

- If drug-related grade 3 or 4 non-hematologic toxicity is attributable to ruxolitinib or dasatinib, dose interruption of that particular drug is required.

- Patients who experience grade 3 drug related non-hematological toxicity may be given a subsequent course one dose level below the previous course, but the patient must have recovered to grade </=1 before institution of the next course.
- If a patient has drug-related grade 4 non-hematological toxicity, he/she may receive a subsequent courses at one reduced dose level after resolution of toxicity to grade </=1, only if approved by the Principal Investigator based on the clinical significance of the toxicity and only if patient has had derived a benefit from the therapy.
- The dose of therapeutic agents can be decreased during a cycle, at the discretion of treating physician, for chronic grade 2 non-hematological toxicity.
- Documentation of the reason(s) study drug is discontinued is required.
- Other dose modifications may be considered as clinically indicated with documentation and approval of the PI.
- Hematological toxicity - Cytopenias are common in the patient population studied in this trial. Dose interruptions or modifications will be made for Grade 4 hematological toxicities, only if the Investigator and the PI strongly feel that the cytopenias are related to ruxolitinib or dasatinib and not related to underlying disease or the use of Hyper-CVAD chemotherapy.
- For patients experiencing toxicities thought to be related to ruxolitinib or dasatinib, the following dose adjustments schema will be used –

Dose level	**Ruxolitinib dose (Adults, Age ≥18 years)**	**Ruxolitinib dose (Pediatric Patients, Age ≥10 and <18 years)**
-2	5 mg twice daily	2.9 mg/m^2 twice daily (Max. 5 mg twice daily)
-1	10 mg twice daily	5.9 mg/m^2 twice daily (Max. 10 mg twice daily)
1 (starting dose)	15 mg twice daily	8.8 mg/m^2 twice daily (Max. 15 mg twice daily)
2	20 mg twice daily	11.8 mg/m^2 twice daily (Max. 20 mg twice daily)
3	25 mg twice daily	14.7 mg/m^2 twice daily (Max. 25 mg twice daily)

Dose level	**Dasatinib dose (Adults, Age ≥18 years)**	**Dasatinib dose (Pediatric Patients, Age ≥10 and <18 years)**

-3	20 mg once daily	11.8 mg/m2 orally once daily (Max. 20 mg daily)
-2	50 mg once daily	30 mg/m2 orally once daily (Max. 50 mg daily)
-1	70 mg once daily	41.2 mg/m2 orally once daily (Max. 70 mg daily)
1 (starting dose level)	100 mg once daily	60 mg/m2 orally once daily (Max. 100 mg daily)

Please see Appendix 2 for the pediatric dosing table.

7.0 CONCOMITANT THERAPY

All concomitant medications will be collected from day 1 through the safety reporting period. All supportive measures consistent with optimal patient care should be provided throughout the study according to the institutional standards.

- Patients should be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator and/or treating physician. At each visit, the patient should be asked about any new medications he/she is or has taken after the start of the study drug. All concomitant medications/significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug should be recorded.
- Ruxolitinib and dasatinib are predominantly metabolized by CYP3A4. Concurrent administration of ruxolitinib or dasatinib and strong CYP3A4 inhibitors (such as ketoconazole, fluconazole, itraconazole, ritonavir) and inducers (such as rifampin, rifabutin) should be avoided.
- If there is no good alternative available for a strong CYP3A4 inhibitor, ruxolitinib and dasatinib dose should be reduced as described in the Prescribing Information for each drug and patients should be closely monitored for potential toxicities.
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided. In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- Nonclinical data demonstrate that the solubility of dasatinib is pH dependent. Long-term suppression of gastric acid secretion by H2 antagonists or proton pump inhibitors (e.g., famotidine and omeprazole) is likely to reduce dasatinib exposure. The concomitant use of H2 antagonists or proton pump inhibitors with dasatinib is not recommended. The use of antacids (at least 2 hours prior to or 2 hours after the dose of dasatinib) should be considered in place of H2 antagonists or proton pump inhibitors.

7.1 Allowed Concomitant Therapy

Intrathecal chemotherapy for CNS prophylaxis/treatment is allowed. Radiotherapy for symptomatic CNS disease is allowed. The use of hematopoietic growth factors or transfusions is allowed. Steroids (up to 40mg/day for 4 days dexamethasone or equivalent) and hydroxyurea is allowed for the first 2 weeks of the study period to control rapidly proliferating disease.

7.2 Prohibited Concomitant Therapy

Patients may not receive other investigational drugs, immunosuppressive medications (except as described in Section 7.1), radiotherapy (except as described in Section 7.1), or systemic anti-neoplastic therapy during the study.

8.0 PRETREATMENT EVALUATIONS

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by the IRB	Within 14 days of study start
Background information	History of present illness, prior cancer history as far as traceable, and relevant past medical/ surgical history	Within 14 days of study start
Physical examination	Vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status (Zubrod)	Within 14 days of study start
Concomitant medications	Document concomitant medications	Within 14 days of study start
Hematology	WBC with differential, unless WBC <0.5 $x10^9$/L in which case differential not needed, Hemoglobin, Platelet count	Within 14 days of study start
Biochemistry	Sodium, chloride, potassium, bicarbonate, alanine aminotransferase (ALT), bilirubin total, creatinine, uric acid, LDH	Within 14 days of study start
Chest X-ray	Evaluation of lung fields and pleural effusion	Within 14 days of study start
Pregnancy test	Perform only in women of child-bearing potential. Pregnancy test can be done in either serum or urine.	Within 14 days of study start
Screening for Hepatitis B, Hepatitis C and HIV		Within 30 days of study start
Bone marrow	Aspirate and/or bone marrow biopsy	Within 30 days of study start
Electrocardiogram	12 lead ECG	Within 30 days of study start
MUGA scan or echocardiogram	Evaluation of ejection fraction	Within 30 days of study start
Optional Correlative studies	Refer to Section 14.0 for details	

9.0 EVALUATIONS DURING THE STUDY

Procedure	Comments	Schedule
Physical exam including toxicity assessment		Weekly for cycle 0, then prior to each cycle
Hematology	CBC with differential (except when WBC less than 0.5), platelet count, hemoglobin	Hematology will be performed 1 to 3 times weekly during the cycle 0 and at least weekly thereafter during the intensive chemotherapy cycles. During the maintenance cycles, Hematology should be performed at least monthly (prior to the start of each cycle)
Clinical Chemistry	Sodium, chloride, potassium, bicarbonate, alanine aminotransferase (ALT), bilirubin total, creatinine, uric acid, LDH	Clinical Chemistry will be performed 1 to 3 times weekly during the cycle 0 and at least weekly thereafter during the intensive chemotherapy cycles. During the maintenance cycles, Clinical Chemistry should be performed at least monthly (prior to the start of each cycle)
Bone Marrow	Aspirate and/or bone marrow biopsy	At the end of cycle 0 (before start of cycle 1), and then before each subsequent cycle. Note: once CR/CRi is achieved, bone marrow will repeated every 2-3 cycle, or as clinically indicated. For patients starting chemotherapy before the end of cycle 0, a marrow will be repeated prior to starting chemotherapy, unless there is a clear evidence of disease progression Consider repeating cytogenetic studies only if abnormal at start. No marrow aspiration is necessary to document response if clearly failing to respond or progressive disease is noted (e.g., circulating blasts).
Chest X-ray	Evaluation of lung fields and pleural effusion	Prior to even number courses (2, 4, 6, 8) of chemotherapy regimen (i.e. courses with high-dose MTX and cytarabine)
Optional Correlative studies	Refer to Protocol Section 14.0 for details	

10.0 STUDY CALENDAR

		Cycle 0			C0D22 (C1D1) and at the start of each subsequent cycle HyperCVAD cycles 1-8 (±3 days)
Study Assessments[1]	**Screen[2]**	**Day 1[2]**	**Day 8 (±3 days)**	**Day 15 (±3 days)**	**Continuation[3]**
Informed Consent	X				
Baseline Demographics	X				
Medical History	X				
Concomitant Medications	X	Continuous			
Physical Exam	X	X	X	X	X
ECOG Performance Status	X	X			X
Vital Signs	X	X	X	X	X
Weight	X	X			X
Height	X				
Hematology, Clinical Chemistry[4,5]	X	X	X	X	X
Screening for Hepatitis B, Hepatitis C and HIV	X[7]				
Pregnancy Test[6]	X				
Chest x-ray	X				X[8]
12-Lead ECG	X[7]				
ECHO or MUGA	X[7]				
Disease Assessment[9]	X[7]				X[10]
Adverse Events		Continuous			
Optional Correlative studies (PB and BM)	X[11]				X[11]

1. Assessments scheduled on days of dosing should be done prior to administration of study drug(s), unless otherwise specified.

		Cycle 0			C0D22 (C1D1) and at the start of each subsequent cycle HyperCVAD cycles 1-8 (±3 days)
Study Assessments[1]	**Screen[2]**	**Day 1[2]**	**Day 8 (±3 days)**	**Day 15 (±3 days)**	**Continuation[3]**

2. Within 14 days before first dose. Screening assessments can be used as day 1 assessments if done within 72 hours.
3. If clinically indicated, assessments during continuation period can occur more frequently.
4. Hematology (WBC with differential, unless WBC <0.5 x10^9/L in which case differential not needed), Hemoglobin, Platelet count); Clinical Chemistry (sodium, chloride, potassium, bicarbonate, alanine aminotransferase (ALT), bilirubin total, creatinine, uric acid, LDH).
5. Hematology and Clinical Chemistry will be performed 1 to 3 times weekly during the cycle 0 and at least weekly thereafter during the intensive chemotherapy cycles. During the maintenance cycles, Hematology and Clinical Chemistry should be performed at least monthly (prior to the start of each cycle)
6. Perform only in women of child-bearing potential. Pregnancy test can be done in either serum or urine.
7. Within 30 days of start of treatment
8. Prior to even number courses (2, 4, 6, 8) of chemotherapy regimen (i.e. courses with high-dose MTX and cytarabine)
9. Disease assessment by bone marrow samples (aspirate and/or biopsy) should be done at screening, end of cycle 0 (before start of cycle 1), and then before each subsequent cycle. Note: Once CR/CRi is achieved, bone marrow will repeated every 2-3 cycle, or as clinically indicated.
10. Note: For patients starting chemotherapy before the end of cycle 0, a marrow will be repeated prior to starting chemotherapy, unless there is a clear evidence of disease progression
11. Peripheral blood and bone marrow will be collected at baseline, at the end of cycle 0 before start of chemotherapy (or earlier if chemotherapy is added before the completion of cycle 0, i.e. before day 21), at the time of CR/CRi, and at the time of relapse.

11.0 CRITERIA FOR RESPONSE

Complete Response (CR)

Disappearance of all clinical and/or radiologic evidence of disease
Neutrophil count ≥ 1.0 x 10^9/L
Platelet count ≥ 100 x 10^9/L
Normal bone marrow differential (≤ 5% blasts)
No extra-medullary leukemia

Complete Remission with Incomplete Blood Count Recovery (CRi)

CR except for ANC < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L

Partial Remission (PR)

Blood count recovery as for CR, but with a ≥50% decrease in the percentage of marrow blasts to >5% to 25% in the bone marrow.

12.0 ADVERSE EVENT REPORTING

Annual reports to the FDA will include a summary tabulation of adverse events by treatment cohort.

12.1 Leukemia-specific Adverse Event Recording and Reporting Guidelines

These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event.
    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed
        i. Hematologic laboratory abnormalities will not be recorded as baseline events for patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
        ii. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
2. The maximum grade of the adverse event will be captured per course or protocol defined visit date.
3. These adverse events will be recorded in the case report form:
    a. Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    b. All serious adverse events regardless of attribution to the study drug(s).
    c. Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
4. Hematologic adverse events will not be recorded or reported for studies in patients with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    a. Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g. marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
5. Serious adverse events will be reported according to institutional policy.
6. Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

12.1.4 Serious Adverse Event Reporting (SAE)

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 drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- 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 for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- 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.

- 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 IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Companies:

All events reported to FDA will also be reported to Incyte Pharmacovigilance representative at email address IncytePhvOpsIST@Incyte.com or fax to Telerx at 866-726-9234 as provided in the Research Agreement within 24 hours of reporting. A copy of the FDA report will also be sent to the Incyte Pharmacovigilance representative as is in other MD Anderson Incyte funded protocols.

13.0 DISCONTINUATION OF STUDY TREATMENT

A patient's treatment with study drugs may be discontinued for any of the following reasons:

- Clinically significant progressive disease
- Failure to achieve CR, CRi or PR after a maximum of 2 induction courses. Patients may continue therapy if deriving clinical benefit after discussion with the Principal Investigator
- Adverse events 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
- Non-compliance with protocol requirements
- Patient's death
- Investigator decision
- Patient decision (e.g., withdrawal of consent)

Patients who discontinue the study treatments will have a follow-up visit 30 days (± 10 days) after the last dose of the study drugs. For patients who cannot come for the clinic visit, a phone call to assess for any side-effects will be done.

14.0 BIOMARKER STUDIES

Collection of research samples will be optional for all patients. Peripheral blood (30 cc) and bone marrow (5 cc) samples will be collected at baseline, at the end of cycle 0 before start of chemotherapy (or earlier if chemotherapy is added before the completion of cycle 0, i.e. before day 21), at the time of CR/CRi, and at the time of relapse. All samples are placed on ice immediately after sample collection. These samples will be stored and processed as following: (1) phospho-signaling studies to assess for modulation of JAK-STAT and cytokine receptor signaling, using multiparametric flow cytometry (to be performed in Dr. Marina Konopleva's lab); (2) RNA sequencing analysis; (3) proteomics profiling; (4) sample storage for xenografting into immunodeficient mice. For xenografting analysis, in Konopleva lab or in the lab of our collaborator Sarah Tasian. For Dr. Tasian, de-identified samples will be shipped to Tasian Laboratory, Attn: JP Loftus, Children's Hospital of Philadelphia, 3501 Civic Center Boulevard, CTRB 3100, Philadelphia 19104; (5) testing of novel agents or combinations in the in vivo generated PDX models. We will also collect remission peripheral blood samples and store these as non-tumor DNA, for possible validation of novel mutations by targeted DNA sequencing.

Additional Optional Pharmacodynamic Assessments. Any leftover sample will be stored for possible additional exploratory pharmacogenetic evaluations. Samples will be stored in Dr. Konopleva's lab.

15.0 STATISTICAL CONSIDERATIONS

It is expected that a maximum total of 92 Ph-like ALL patients will be enrolled in this phase I-II study. 18 patients in the phase I study for ruxolitinib cohort (Cohort A), and 40 patients will be enrolled in each of the cohorts in phase II portion (for cohort A, 6 patients treated in the MTD level in phase I will be included in the phase II).

Phase I

The primary objective of the phase I portion of the study is to determine the MTD for ruxolitinib in combination with chemotherapy in patients with Ph-like ALL. The 3+3 algorithm in the following table will be used to guide dose escalation/de-escalation. Dose limited toxicities (DLTs) in ruxolitinib monotherapy and in the first cycle of the combination treatment will be used for dose escalation. The MTD is defined as the highest dose level at which no more than 1 out of 6 patients experience a DLT. Once the MTD is determined, phase II portion for the ruxolitinib cohort will start. For this phase I study, a maximum of 18 patients will be enrolled. The 6 patients treated at the MTD dose level will be included in the phase II portion of this cohort.

Table: 3+3 algorithm for guidance of dose escalation

Number of patients with DLT at a given dose	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next higher dose level
1 out of 3	Enter 3 additional patients at this dose level • If 0 of these 3 patients experience DLT, proceed to the next higher dose level. • If 1 or more of this group suffer DLT, this dose exceeds the MTD and dose escalation is stopped. Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose level.
≥2	Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
MTD: The highest dose at which no more that 1 of 6 patients has had a DLT. Six patients should be treated before the dose is declared MTD	

Phase II

It is expected that a maximum total of 80 Ph-like ALL patients will be enrolled in this phase II portion of the study with 40 patients being in each of the cohorts, cohort A (up to 34 additional patients in cohort A by including 6 patients treated at the MTD in the phase I portion of the study) and cohort B (Table 1), with the expectation of 34 patients having assessments of the response. Patients who drop out of study early without completing cycle 2 due to excessive toxicity or progressed disease/death will be counted as treatment failure for the primary efficacy analysis. Otherwise patients who drop out of study early without completing cycle 2 and without the response evaluated due to other reasons will be replaced. All patients will be registered through the Clinical Oncology Research System (CORe) at MDACC, and the estimated accrual rate is approximately 2 patients per month. A patient will be considered as having cycle 2 completed if the patient is available for the assessment of response (section 11) at the end of cycle 2.

The primary objective of this study is to assess efficacy in terms of complete response (CR/CRi) during the first 2 cycles. The Optimum two-stage design proposed by Simon[57] will be implemented in each of the cohorts separately. For each cohort, a target CR/CRi of 25% will be assumed and a CR/CRi of 10% or lower will be considered as not desirable. The type I error and power will be set to 0.10 and 0.80 respectively. Under these specifications, we will enroll 13 patients, and will not enroll new patients until enough responders are observed to warrant further enrollment within

each cohort. If some patients among these 13 patients do not have assessments of the response, we will continue the accrual to replace such patients. The evaluation of the efficacy in the first stage will be performed when the first 13 patients have assessments of the response within each cohort. If no more than 1 patient out of these 13 patients achieves CR/CRi within a cohort, then the enrollment of patients into that cohort will be halted. If 2 or more out of these 13 patients achieve CR/CRi, then the accrual will continue until a total of 34 patients have been enrolled within each cohort. If some patients among these 34 patients do not have assessments of the response, we will continue the accrual to replace such patients. The evaluation in the second stage will be performed when the first 34 patients within each cohort have assessments of the response. For each cohort, if 6 or more out of these 34 patients achieve CR/CRi, the treatment of that cohort will be considered efficacious and is worth further investigation. Under this criteria based on the Simon's Optimum two-stage design, the per-cohort probability of early termination is 62% if the true ORR is 10% and the expected sample size is 21 patients for each cohort. Considering potential loss to follow-up, a maximum total of 40 patients will be enrolled in each cohort.

The method of Thall, Simon and Estey[58] will be used for toxicity monitoring for this study. Toxicity will be monitored among the 40 patients for each cohort. Denote the probability of toxicity by p(T), where toxicity is defined as any ruxolitinib- related or dasatinib-related grade 4-5 anemia, neutropenia or thrombocytopenia lasting more than 14 days or grade 3-5 organ toxicity (neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, cutaneous) and occurs anytime during the treatment. We assume as a priori, p(T) ~ beta (0.6, 1.4). We will stop the trial if $Pr(p(T)> 0.30 \mid data) > 0.8$. That is, we will stop the trial for new patient enrollment if at any time during the study that there is more than 80% chance that the toxicity rate is more than 30%. This toxicity stopping monitoring rule will be applied by cohort size of 5, starting from the 5th patient. Stopping boundaries corresponding to this stopping monitoring rule are listed in Table 2. The operating characteristics are summarized in Table 3. Multc Lean Desktop (version 2.1) was used to generate the toxicity stopping boundaries and the OC table.

Table 2. Early stopping boundaries for toxicity monitoring

# of patients (in cohort size of 5, starting from the 5th patient)	Stop the trial if there are this many patients with toxicities:
5	3-5
10	5-10
15	7-15
20	8-20
25	10-25
30	12-30
35	13-35

Table 3. Operating characteristics for toxicity monitoring

True toxicity rate	Prob(stop the trial early)	Average sample size
0.20	0.10	37.09
0.25	0.22	33.98
0.30	0.40	29.50
0.35	0.62	24.18
0.40	0.80	18.96

Since there is little evidence to suggest that single-agent dasatinib or single-agent ruxolitinib would be expected to be of benefit in the treatment of patients with relapsed or refractory ALL, a futility monitoring for the monotherapy part in each cohort will be performed. Specifically, we will take three looks when every 10 patients are enrolled and evaluated for the single agent cycle within each cohort. For each look, if more than 20% of cumulative subjects' progress during cycle 0, the single-agent cycle will be deleted from the cohort.

15.1 Analysis Plan

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The response rate (CR/CRi) will be estimated along with the confidence interval in each cohort. The estimation will be performed in 34 patients who are included for the two stage design, and also in all patients who received any treatment by counting patients who drop out the study early without evaluation of the primary outcome as treatment failures. Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who enter the study and do not take any of the study drugs and have this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. Time to event outcomes including duration of response and progression-free survival will be estimated using the Kaplan-Meier method, and the association of the time to event outcomes with patient characteristics will be evaluated using the log rank test and Cox proportional hazards regression analysis.

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Appendix 1: Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5 are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below.

Inhibitors of CYP3A4/5	Inducers of CYP3A4/5
Strong inhibitors: INDINAVIR NELFINAVIR RITONAVIR CLARITHROMYCIN ITRACONAZOLE KETOCONAZOLE NEFAZODONE SAQUINAVIR SUBOXONE TELITHROMYCIN **Moderate inhibitors:** aprepitant erythromycin diltiazem fluconazole grapefruit juice Seville orange juice verapamil **Weak inhibitors:** cimetidine **All other inhibitors:** amiodarone NOT azithromycin chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate	Carbamazepine Efavirenz Nevirapine Barbiturates Glucocorticoids Modafinil Oxcarbarzepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's Wort Troglitazone
fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit telaprevir voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Appendix 2: Dosing Chart for Pediatric Patients

DOSING CHART FOR PEDIATRIC PATIENTS

Ruxolitinib (5mg tablets)						
BSA		**Dose level 3**	**Dose level 2**	**Dose level 1**	**Dose level -1**	**Dose level -2**
		14.7 mg/m^2 twice daily	**11.8 mg/m^2 twice daily**	**8.8 mg/m^2 twice daily**	**5.9 mg/m^2 twice daily**	**2.9 mg/m^2 twice daily (5.8 mg/m^2/day)**
low BSA	**high BSA**	**Dose**	**Dose**	**Dose**	**Dose**	**Dose**
0.8	0.92	10mg AM / 15mg PM	10mg twice daily	5mg AM / 10mg PM	5mg twice daily	5mg *daily*
0.93	1.05	15mg twice daily	10mg AM / 15mg PM	5mg AM/ 10mg PM	5mg twice daily	5mg *daily*
1.06	1.18	15mg AM / 20mg PM	10mg AM / 15mg PM	10mg twice daily	5mg AM / 10mg PM	10mg *daily* MWF / 5mg *daily* TThSaSu
1.19	1.31	15mg AM/ 20mg PM	15mg twice daily	10mg twice daily	5mg AM / 10mg PM	10mg *daily* MWF / 5mg *daily* TThSaSu
1.32	1.44	20mg twice daily	15mg AM / 20mg PM	10mg AM/ 15mg PM	5mg AM / 10mg PM	5mg *daily* MWF / 10mg *daily* TThSaSu
1.45	1.57	20mg AM / 25mg PM	15mg AM / 20mg PM	10mg AM / 15mg PM	10mg twice daily	5mg twice daily or 10mg *daily*
1.58	1.73	25mg twice daily	20mg twice daily	15mg twice daily	10mg twice daily	5mg twice daily or 10mg *daily*

Dasatinib (20mg, 50mg, 70mg, 100mg tablets)					
BSA		**Dose level 1**	**Dose level -1**	**Dose level -2**	**Dose level -3**
		60 mg/m^2 daily	**41.2 mg/m^2 daily (288.4mg/m^2/week)**	**30 mg/m^2 daily (210mg/m^2/week)**	**11.8 mg/m^2 daily (82.6mg/m^2/week)**
low BSA	**high BSA**	**Dose**	**Dose**	**Dose**	**Dose**
0.8	0.92	50mg daily	20mg MWF / 40mg TThSaSu	20mg M-F / 40mg SaSu	20mg TThSaSu only
0.93	1.05	60mg daily	40mg daily	20mg MWF / 40mg TThSaSu	20mg TThSaSu only
1.06	1.18	70mg daily	40mg MWF / 50mg TThSaSu	40mg M-F / 20mg SaSu	20mg M-F only
1.19	1.31	80mg daily	50mg daily	40mg daily	20mg M-F only
1.32	1.44	80mg daily	50mg MWF / 60mg TThSaSu	40mg daily	20mg M-Sa only
1.45	1.57	90mg daily	60mg daily	40mg MWF / 50mg TThSaSu	20mg daily
1.58	1.73	100mg daily	70mg daily	50mg daily	20mg daily

MWF: Monday, Wednesday, Friday; SaSu: Saturday, Sunday; M-F: Monday through Friday; TThSaSu: Tuesday, Thursday, Saturday, Sunday; M-Sa: Monday through Saturday