Innovative Treatment Approaches for Patients with ALL

INTRODUCTION
Acute lymphoblastic leukemia (ALL) is characterized by clonal proliferation of lymphoid progenitors. Significant advances have been made in the last decade toward understanding the disease pathogenesis, refinement of prognostic groups and development of novel therapies that target specific subsets of ALL. These risk-adapted therapies are transforming the treatment strategies for adults with ALL and are beginning to result in significant improvements in survival. With the current treatment regimens, long-term survival is achieved in approximately 50% of patients with B-cell ALL, 50%-60% with Philadelphia-chromosome-positive ALL, 80% with Burkitt’s leukemia, and 60% with T-ALL.

In this month’s Leukemia Insights, written by Dr. Elias Jabbour and sponsored in part by the Betty Foster Leukemia Research Grant, we discuss innovative treatment approaches for patients with acute lymphoblastic leukemia (ALL).

FRONTLINE TREATMENT

PRE-B CELL AGE <30 YEARS
Adolescent and young adult (AYA) patients can receive treatment with either pediatric-based chemotherapy regimens or with the R-Hyper CVAD regimen designed for adults.

AUGMENTED BFM IN COMBINATION WITH OFATUMUMAB
For AYA patients, the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) tested the concept of pediatric-inspired regimen in patients up to the age of 60. When compared to historical data, the pediatric-inspired regimen was found to significantly improve OS (66% versus 44%; p < 0.001) primarily in patients up to the age of 45.

At our institution, the augmented Berlin-Frankfurt-Munster (augmented BFM) regimen has induced a CR rate of 93% and MRD negativity of 83%, with 5-year CR duration and survival rates of 53% and 60%, respectively. These results were similar to the R-HCVAD in a similar population.

Ofatumumab is a second-generation anti-CD20 monoclonal antibody

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that binds to a site different than rituximab. Ofatumumab targets a monoclonal antibody that is directed against the small-loop epitope on the CD20 molecule, and is more potent than rituximab. The combination of HCVAD with ofatumumab was found to be highly effective and is now our frontline therapy for AYA patients with ALL. A clinical trial testing the combination of augmented BFM with ofatumumab is ongoing.

PRE-B CELL AGE 30-59 YEARS

Patients in this age group have several options, described below.

HYPER-CVAD + OFATUMUMAB

Forty-eight patients with de novo pre-B CD20-positive ALL have been treated so far. Ofatumumab is given as 2 g/m2 twice per week in the first 4 courses. The rates of CR and minimal residual disease negativity were both 97%. With a median follow-up of 15 months, the two-year progression-free and overall survival rates are 76% and 87%, respectively. This trial allows patients with pre-B-ALL, Philadelphia negative, CD20-positive ( REGARDLESS OF THE LEVEL OF EXPRESSION). This trial is ongoing.

HYPER-CVAD + LIPOSOMAL VINCristine

Twenty-nine patients have been treated so far (19 of them Philadelphia positive). The CR rate is 96%. The MRD negativity is 89%. Median follow-up is 22 months. The two-year complete remission duration and overall survival rates are 87% and 68%, respectively. This trial allows patients with precursor-B or T lymphoblastic leukemia or lymphoblastic lymphoma. Patients with CD20 expression above 20% can also receive rituximab. Liposomal vincristine is given at the dose of 2 mg/m2 IV on D1 and D8 during odd cycles. Patients with Philadelphia-positive ALL can receive additional tyrosine kinase inhibitors.

HYPER-CVAD + BlinatumomAb

A Phase III randomized trial (TOWER study) compared blinatumomab to investigator’s choice chemotherapy in patients with relapsed/refractory ALL. More than 400 patients with relapsed/refractory Philadelphia-negative ALL were randomized to either blinatumomab (n=271) or standard of care chemotherapy (n=134). The overall response rates were 45% and 30% (p=0.007), respectively. Molecular remission rates among responders, defined as <10^5 blasts in the first 12 weeks, were 75% and 48%, respectively. The median overall survival was 7.7 months (5.6-9.6) with blinatumomab and 4.0 months (2.9-5.3) with standard of care chemotherapy, respectively (p=0.012, HR=0.71). The toxicity profile of blinatumomab was acceptable, consisting of fever, chills, and hypogammaglobulinemia. Due to the high efficacy of blinatumomab in eradicating minimal residual disease (MRD) and its high efficacy in relapsed/refractory disease, a sequential combination of hyper-CVAD with blinatumomab may optimize the rate of MRD negativity and subsequently improve the cure rates of adult patients with B-cell ALL while minimizing toxicities encountered with chemotherapy. A Phase II study combining the sequential combination of blinatumomab and chemotherapy in newly diagnosed B-ALL is ongoing at our institution. Patients will receive a total of 4 cycles of HCVAD alternating with HDAC/MTX (2 each) followed by 4 cycles of blinatumomab and one year of POMP maintenance therapy. The study is active and accruing Philadelphia-negative pre-B ALL.

ELDERLY (≥ 60 YEARS)

The incidence of ALL increases after the age of 50 years. Different approaches have been applied in this patient cohort. In elderly patients with ALL (defined as older than 55-60 years), intensive chemotherapy results in a CR rate of 80% with high rate of toxicities. One-third of patients achieving CR may die of myelosuppression-associated complications during consolidation-maintenance. The long-term cure rate among such patients is only 15% to 20%. The GOMALL reported a CR rate of 70%, an early death rate of 14%, a mortality of 6% in CR, and 5-year survival rates of 23% in 268 elderly patients treated with less intensive induction and consolidation regimen. The goal with modern regimens is to maintain efficacy but reduce toxicity.

MINI-HYPER-CVAD + INOTUZUMAB

Inotuzumab ozogamicin is a CD22 monoclonal antibody that is covalently linked to calicheamicin, a potent cytotoxic agent that causes a break between double stranded DNA. In a Phase II study, 38 patients (median age 69 years, range 62-79) with newly diagnosed Philadelphia-negative ALL were treated with inotuzumab plus mini-HCVD (low doses of hyperfractionated cyclophosphamide, vincristine, and dexamethasone alternating with low doses of methotrexate and high-dose cytarabine), a low intensity chemotherapy (no anthracycline, 50% dose reduction of steroid and cyclophosphamide, 75% dose reduction of methotrexate, and 83% dose reduction of cytarabine). Inotuzumab was administered during the first 4 courses of mini-HCVD during course 1 followed by 1 mg/m2 once during each course 2. The objective response rate was 97% (CR rate of 80%). All patients in CR also achieved MRD negativity. The 2-year CR and OS rates were 81% and 64%, respectively. The 2-year survival rates were higher with mini-HCVD plus inotuzumab than historical Hyper-CVAD plus rituximab (64% vs. 38%, respectively). This trial is ongoing.

T-CELL

Nalereimab is a prodrug of ara-G and produces cytotoxic levels of ara-GTP in circulating leukemia cells. It has been demonstrated that ara-GTP is accumulated at higher levels in T lymphoblasts than in myeloblasts or B lymphoblasts.

HYPER-CVAD + NELARABINE

We assessed nelarabine in combination with HCVAD in 48 patients (median age: 38 years) with newly diagnosed T-ALL and 36 with T-cell lymphoblastic lymphoma. Nelarabine, dosed at 650 mg/m2 IV daily for 5 days, was administered either after or during consolidation chemotherapy. Peripheral neuropathy of Grade 2 or less was observed in 55% of patients treated with the combination of HCVAD and nelarabine, and was reversible in all. With 41-month median follow up, the 5-year survival rate was 66% (for AYA ≤ 40 years, it is 70%). For patients with early T-cell precursor ALL (ETP-ALL) and mature T-ALL, the rates were 39% and 54%, respectively. Anti-ALL therapy followed by allogeneic stem cell transplantation is recommended in first remission in adult patients with ETP-ALL. The addition of myeloablative-directed therapies might also improve the outcome of ETP-ALL. Newer agents targeting NOTCH1, FLT3, IDH1, and IDH2 mutations are being explored. The study is ongoing and accruing patients with newly diagnosed T-ALL.

BURKITT LEUKEMIA

Burkitt’s leukemia/lymphoma is an aggressive, mature B-cell neoplasm characterized by translocation of the MYC gene. The addition of rituximab to standard chemotherapy has been shown to improve outcomes in patients with Burkitt’s leukemia.

DOSE-ADJUSTED EPOCH + OXATUMUMAB/RITUXIMAB

A pilot study investigated dose adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in combination with rituximab in 30 patients (median age: 13 years; age >40 years, 40%) with Burkitt disease. The progression-free and overall survival rates were 95-100% and 90-100%, respectively. Of note, the majority of patients (90%) were of low- and intermediate-risk disease. Doublehit and triple-hit lymphomas harbor concurrent rearrangements of MYC and BCL2 and/or BCL6; they are associated with a very aggressive course and poor clinical outcome. They are characterized typically by high tumor proliferation and likely require Burkitt lymphoma-type strategies. One challenge in this respect is that most patients with these diseases are older than 60 years and generally have poor tolerability of regimens typically used in Burkitt lymphoma. Dose adjusted EPOCH in combination with rituximab/oxtatumumab is ongoing for patients with newly diagnosed mature B-cell ALL. The study is open as well for patients with relapsed/refractory disease.

PHILADELPHIA CHROMOSOME POSITIVE ALL

The combination of cytotoxic chemotherapy with tyrosine kinase inhibitor (TKI) has become the standard of care in patients with Philadelphia-positive ALL. The best results are achieved when TKIs are incorporated early, daily, and continuously with chemotherapy. TKIs should be started immediately upon recognition of Philadelphia-positive disease, and prolonged continuous exposure to TKIs is superior to pulsed or intermittent administration.
HYPER-CVAD + PONATINIB

Although TKIs showed promising activity in patients with Philadelphia-positive ALL, many patients relapse with a T315I clone resistant to imatinib and second-generation TKIs. Ponatinib is a more potent third-generation BCR-ABL1 TKI that additionally suppresses the T315I clones. In a phase 2 single arm trial, 53 patients with Philadelphia-positive ALL received combined-modality therapy combining ponatinib and HCVAD. Initially, ponatinib was given at 45 mg daily, but the study was amended after the occurrence of 2 fatal myocardial events. Therefore, ponatinib was given at 45 mg daily for 14 days during induction, then continuously at 30 mg daily, with the dose reduced to 15 mg daily once a complete molecular remission (CMR) was obtained, since then no further vascular events were reported. The complete response, complete cytogenetic response, major molecular response, and CMR rates were 100%, 100%, 98%, and 79%, respectively. With a median follow-up of 33 months, the complete remission duration and overall survival rates were 82% and 80%, respectively. The clinical efficacy of HCVAD and ponatinib was compared to that of HCVAD and dasatinib in a propensity score matching analysis. The clinical outcome of HCVAD plus ponatinib appeared superior to that of HCVAD plus dasatinib in patients with Philadelphia-positive ALL. The 3-month CMR rates were 82% and 65% (p=0.03), respectively. The 3-year event-free and overall survival rates were 69% and 46% (p=0.04) and 83% and 56% (p=0.03), respectively. The trial is open for patients with newly diagnosed Philadelphia-positive ALL, including patients who have received one cycle of chemotherapy.

BILNUTUMOMAB AND PONATINIB

Bilnatumomab, a bispecific T-cell engaging antibody (BiTE) that links CD3 T-cell receptor to CD19 on B-cells, was also evaluated in a Phase II ALCANTARA trial in patients with relapsed/refractory Philadelphia-positive ALL. Bilnatumomab was given at standard dose for up to 5 cycles in 45 patients; after the first two cycles, 36% of patients achieved CR or partial hematologic response. With a median 3-year follow-up, 81% of patients were able to achieve a complete hematologic remission. Among the 16 responders, the MRD negativity rate was 88%, and 44% of patients were able to achieve an allogeneic stem cell transplant. Bilnatumomab is superior to standard chemotherapy in patients with relapsed/refractory ALL, and showed significant activity as monotherapy in Philadelphia-positive ALL. The drug has an excellent safety profile with minimal myelosuppression. Ponatinib is the most potent TKI: when combined with chemotherapy, it induced the highest CR rate, but with no resistant mutations so far reported. Therefore, the combination of bilnatumomab with ponatinib may further improve the CR and survival rates compared with chemotherapy and TKI combination with significantly better safety profile. A trial combining bilnatumomab and ponatinib is being investigated for elderly patients (≥60 years) with newly diagnosed Philadelphia-positive ALL. Patients will receive 4-5 cycles of bilnatumomab administered concomitantly with ponatinib at 30 mg daily with reduction to 15 mg once a CMR is achieved. Ponatinib will be given indefinitely. The study will be open as well for all adults with relapsed/refractory Philadelphia-positive ALL.

MINI-HYPER-CVAD + PONATINIB

The results remain poor in older patients (≥60 years) with Philadelphia-positive ALL because of poor tolerance of intensive chemotherapy, mortality with intensive chemotherapy, and lack of access to allogeneic stem cell transplant. Older patients are predisposed to severe toxicity from conventional chemotherapy, which is associated with high mortality rate during consolidation and maintenance despite achieving CR.

The phase 2 clinical trial of hyper-CVAD and ponatinib in patients with Ph-positive ALL has shown significant clinical activity that compares favorably to results from previous trials using imatinib or dasatinib. Given previous experience that full-intensity hyper-CVAD results in unacceptable toxicity in many older patients with ALL, there is a rationale to combine ponatinib with a less intensive chemotherapy backbone in patients with Ph-positive ALL. Previous data of the combination of mini-hyper-CVAD with imatinib or ozogamicin in patients with Ph-negative ALL suggests that this dose-reduced chemotherapy backbone can result in excellent response rates with minimal toxicity. Taken together, these studies provide a strong rationale for a phase 2 trial combining ponatinib with mini-hyper-CVAD in patients with Ph-positive ALL, both in the frontline setting and in patients with relapsed/refractory disease. The study is about to be activated for elderly patients (≥60 years) with newly diagnosed Ph-positive ALL as well as adults of all ages with R/R disease.

MIXED-PHENOTYPE ACUTE LEUKEMIA (MPAL)

The definition of mixed phenotype acute leukemia (MPAL) has evolved over the years, but most now accept the WHO definition first published in 2008 and recently in 2016. The essential feature of MPAL is that cells express lineage-specific myeloid markers as well as lineage-specific T- or B-lymphoid markers. There is no standard therapy for patients diagnosed with MPAL; this presents a clinical challenge that has not been well studied. The limited available data suggest that an "ALL-like" or hybrid (ALL/acute myeloid leukemia) regimen followed by allogeneic stem cell transplantation may be advisable. A prospective phase II study assessing a hybrid regimen combining clofarabine, idarubicin, cytarabine, vincristine, and dexamethasone in adult patients with MPAL is ongoing.

CLOFARABINE, IDARUBICIN, CYTARABINE, VINCristine, AND Corticosteroid 1/- RITUXIMAB

We designed a clinical trial using a hybrid regimen of AML and ALL therapies to treat patients diagnosed with MPAL. The backbone of the regimen is our standard induction for AML using clofarabine, idarubicin, and cytarabine administered at attenuated doses. All three of these drugs also have activity in ALL. Vincristine and corticosteroids are added to the regimen for enhanced lymphoid activity. This combination of drugs is reasonable because the toxicity profiles do not overlap, allowing us to safely give all five agents during the same course of therapy. Rituximab or ofatumumab are added in patients who are CD20 positive. Furthermore, intrathecal chemotherapy is administered as well. The trial is currently open for patients with de novo and relapsed MPAL.

MINIMAL RESIDUAL DISEASE

Persistence or reappearance of MRD after induction chemotherapy is the most important adverse prognostic factor in patients with ALL and identifies chemotherapeutic disease. More than 90% of patients who have persistent MRD after chemotherapy experience a clinical relapse, despite continued chemotherapy, with a median time to relapse of 4.5 months. A meta-analysis of a series of 326 adolescent and adult patients with high-risk Philadelphia chromosome-negative ALL treated in the PETHMA ALL-AR03 trial showed poor MRD clearance defined as levels 2.1 x 10^-6 after induction and 5.5 x 10^-6 after early consolidation by flow-cytometry as the only prognostic factor for disease-free and overall survival.

BILNUTUMOMAB

Bilnatumomab, a bispecific T-cell engaging (BiTE) antibody represents the first agent in a class that redirects T-cells to cell surface antigen-expressing cancer cells. Gögebü et al. assessed single agent bilnatumomab in 116 patients with ALL in CR but with MRD positivity. Most patients had ≥ 3 courses of chemotherapy and > 35% were in CR2. Bilnatumomab was given at 15 mg/m^2/day continuous infusion for 28 days every 6 weeks for 4 cycles. Approximately
78% achieved MRD negativity after one cycle and 80% after 4 cycles. With a median follow-up of 29 months, the median OS was 36 months and the RFS was 19 months. The median OS for those who achieved MRD negative status was 40 months versus 12 months for those who remained MRD positive. Notably, allogeneic stem cell transplantation did not confer a survival benefit for patients who achieved MRD negative in first remission. These results provide evidence that a strategy of MRD-directed therapy using monoclonal antibodies is useful in improving outcomes in ALL.

A phase II study of blinatumomab in patients with B-cell lineage ALL in first or second complete remission with positive minimal residual disease is active and ongoing at our institution. Patients will have MRD assessed by 6-color multiparameter flow cytometry and next generation sequencing at baseline, at the achievement of CR and every 3 months thereafter. Early results confirm the findings of the BISTAL trial with an objective response of 80%.

**SALVAGE TREATMENT**

**NEW MONOCLONAL ANTIBODIES IN PRE-B ALL**

Almost all pre-B ALL cells express CD19 and CD22. Several monoclonal antibodies target CD19 and CD22, and have shown high activity in refractory and relapsed ALL.

**INOTUZUMAB OZOGAMICIN**

Inotuzumab ozogamicin is an anti-CD22 monoclonal antibody conjugated to calicheamicin, which is a natural product of micrococca monomorpha echinompoora and is significantly more toxic than chemotherapy. It binds to the minor DNA groove and causes double-strand DNA breaks resulting in cell apoptosis. Inotuzumab binds to CD22 with subnanomolar affinity, is rapidly internalized and delivers the conjugated calicheamicin intracellularly. We conducted two studies of inotuzumab in refractory-relapsed ALL, one with 1.3-1.8 mg/mkg single dose every 3-4 weeks (n=9), and a second with a weekly dose (0.8 mg/mkg in day 1, 0.5 mg/mkg on day 9 and 15, every 3 weeks) (n=41). In the 90 patients treated, the narrow CR rate was 40%. The median survival was 6.3 months. These encouraging results led to an international study comparing weekly inotuzumab to standard ALL chemotherapy (FLAG-AT) in ALL salvage 1-2. The objective response rates were 81% and 33%, respectively. Among responders, the MDR-negative rates were 78% and 28%, respectively. The median progression-free survival was 7.7 versus 1.8 months (p<0.001), respectively. The median overall survival was 7.7 versus 6.7 months (p=0.02), respectively. Currently we are exploring combination and lower doses of Inotuzumab approaches in patients with relapsed-refractory disease.

**LOW-DOSE INOTUZUMAB (0.9 MG/ML)**

Due to the occurrence of veno-occlusive disease (VOD) in patients treated with inotuzumab, at the rate of 10%, a lower dose schedule is being explored. Patients with relapsed/refractory CD22 positive ALL will receive inotuzumab at 50% dose reduction (0.6 mg/mkg on D1 and 0.3 mg/mkg on D8) with narrow assessments on Day 14 and 21 and cycle 2 to be resumed between Day 21 and 28. The study is expected to start accrual by the fourth quarter of 2016.

**CHIMERIC ANTIGEN RECEPTOR T-CELLS (CAR T-CELLS) THERAPIES**

CAR T-cells are genetically modified autologous T lymphocytes engineered to express binding sites of specific antibodies, such as a receptor against CD19. These T-cells, harnessed from the patient’s own immune system, target the malignant cells expressing the appropriate antigens. First generation CAR T-cells were studied in B-cell malignancies expressing CD20 or CD19; however, these cells lacked antitumor activity. Subsequently, second and third generation CAR T-cells were created with co-stimulatory domains that improved their expansion and persistence in vivo. In fourth generation CAR T-cells, cytokines or costimulatory ligands were added to increase the expansion and longevity. Since then, there have been several modifications to optimize cytokatic activity while minimizing toxicity.

Fifty nine children with relapsed/refractory ALL were treated with CAR-T cells at the University of Pennsylvania and The Children’s Hospital of Philadelphia. The CR rate was 93%. With a median follow-up of 12 months, the 1-year event-free and survival rates were 59% and 79%, respectively. Cytokine release syndrome (CRS) occurred in 88% of the patients, all of whom recovered. Park and colleagues conducted a similar study with CAR T-cells in adults with refractory/refractory ALL. Of the 46 patients (median age, 45 years) enrolled, all but one were evaluable for response. The CR and MDR negativity rates were 82% and 84%, respectively. The median overall survival was 9 months (0.6 months in CR patients). Severe CRS was observed in 24% of the cases. Lee and colleagues recently reported updated results of 39 children and young adults with relapsed/refractory ALL who received CAR T-cells. The overall CR rate was 59%. Of the 20 patients achieving an MRD-negative CR, the median leukemia-free survival was 18 months, and the 18-month leukemia-free survival 45%. Grade 4 CRS occurred in 16% of the first 21 patients treated.

**THE ROCKET STUDY**

This is a phase 2, single-arm, multicenter trial to determine the efficacy and safety of JCAR015 in adult patients with relapsed or refractory B-cell ALL. Using this approach, autologous T cells can be genetically modified to target leukemia cells through the expression of recombinant vector-encoded genes encoding CD19-specific CARs. The clinical experience to date with CD19-directed CAR T cells generally, and with JCAR015 specifically, has shown this therapy to have potent anti-leukemia activity in both adult and pediatric patients.

Adult patients with relapsed or refractory disease, defined as: a) first or greater bone marrow relapse from CR, or b) any bone marrow relapse after allogeneic stem cell transplantation, or c) refractory ALL, defined by not having achieved a CR or CRi after two attempts at remission induction using standard chemotherapeutic regimens, or d) Ph+ B-cell ALL if subjects are intolerant to or ineligible for TKI therapy, or have progressed despite at least one line of TKI therapy are eligible. The study is currently active.

**THE ZUMA-3 STUDY: A PHASE 1/2 MULTI-CENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF KTE-C19 IN ADULT PATIENTS WITH RELAPSED/REFRACTORY B-ALL**

During phase I, approximately 6-12 patients with high burden (BM blasts>25% or 3 x 10^6 blasts/mm^3 in the peripheral circulation) R/R ALL disease will be enrolled to evaluate the safety of KTE-C19. If the initial KTE-C19 dose is determined to be safe, the study may proceed to phase 2. During phase 2, approximately 50 patients will be enrolled to evaluate the efficacy and safety of KTE-C19. The study is active. We are expecting to transition to the phase 2 part in the very near future.

**PHILADELPHIA CHROMOSOME-LIKE ACUTE LYMPHOBластIC LEUKEMIA**

Two independent groups identified a major subtype of ALL that possesses a gene expression profile and alteration of B231 gene similar to that of BCR-ABL1 ALL but which lacks the BCR-ABL1 fusion protein. It is also associated with a poor prognosis similar to Philadelphia chromosome positive ALL. This entity is now referred to as Philadelphia chromosomelike ALL or BCR-ABL1-like ALL. The frequency of Philadelphia chromosomelike ALL is high, particularly with increasing age from early childhood to young adulthood: 11% in standard-risk and 14% in high-risk childhood ALL, 21% in adolescents and 27% in young adults. Multiple chromosomal rearrangements, sequence mutations, and structural genetic alterations activate cytokine receptors and tyrosine kinase pathways in Philadelphia chromosomelike ALL. Almost half of the cases have rearrangement of cytokine receptor-like factor 2 (CR2L2), encoding a component of the receptor for thymic stromal lymphopoietin (TSLP). It is presented either as a translocation to the immunoglobulin heavy chain enhancer region at 14q12.33 (IGH-CR2L2) or as a focal deletion upstream of CR2L2 resulting in the expression of a PIRB8-CR2L2 fusion transcript, or as a CR2L2 F332C mutation. As a result, there is an overexpression of CR2L2 mRNA and protein. Approximately half of the CR2L2-rearranged cases have activating mutations of Janus kinases, particularly JAK2, but also JAK1 and JAK3. Next generation sequencing identified a diverse range of chimeric fusions involving tyrosine kinases in cases without CR2L2 rearrangement. The genetic alterations deregulate multiple pathways, including ABL1-class chromosomal rearrangements (ABL1, ABL2, CSF1R, and PDGFRB) fusions sensitive to ABL-class tyrosine kinase inhibitors such as dasatinib and imatinib; ETN6T9K3 fusion to ALK kinase
inhibitors (e.g., crizotinib); and those with EPOR, IL-7R, and JAK2 rearrangements (mutations and fusions) sensitive to JAK kinase inhibitors (e.g., ruxolitinib). In conclusion, the genomic profiling in ALL identifies new prognostic markers (e.g., IKZF1), new therapeutic targets (e.g., JAK3), and novel ALL subtypes. These may be amenable to targeted therapies that can improve the adverse prognosis of Philadelphia chromosome-like ALL. Treatment regimens combining chemotherapy and TKIs are ongoing in newly diagnosed and relapsed/refractory Philadelphia chromosome-like ALL. A Phase II assessing the combination of ruxolitinib or dasatinib with chemotherapy in patients with relapsed/refractory Philadelphia chromosome-like ALL is currently open. Patients who have CRLF2 overexpression by flow will be eligible for the ruxolitinib arm (irrespective of the JAK2 mutation status). Patients without CRLF2 overexpression will be assessed for the fusion assay. Depending on the fusion results, the patient may be eligible for the ruxolitinib (JAK2 fusions), or dasatinib (ABL1, ABL1 fusions).

**OTHER NOVEL TREATMENT STRATEGIES**

LY3039478 (a potent Notch inhibitor) in combination with dexamethasone in T-cell lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) - Notch mutations are well characterized and implicated in hematologic malignancies such as T-ALL.

In the phase 1 portion of the study, we aim to determine the recommended dose of LY3039478 in combination with dexamethasone in adult patients with relapsed/refractory T-ALL or T-cell lymphoblastic lymphoma. In the phase 2 portion, we aim to determine if the overall remission rate in adult patients with relapsed/refractory T-ALL/T-LBL treated with LY3039478 in combination with dexamethasone exceeds that of those patients treated with placebo in combination with dexamethasone.

**ADCT-402 - ADCT-402** is an antibody drug conjugate (ADX) composed of a humanized monoclonal antibody directed against human CD19, conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytosine, through a protease cleavable valinealanine linker. The PBD dimers are highly efficient anticancer drugs that bind in the minor groove of DNA and form cytotoxic DNA interstrand cross-links. The potential for ADCT-402 in treating B-cell malignancies was tested in severely combined immunodeficiency (SCID) mice, subcutaneously or intramuscularly implanted with cells from human-derived B-cell leukemia and lymphoma cell lines. Complete responses were observed in mice after receiving a single low dose of ADCT-402. The efficacy of ADCT-402 in these models is due to targeted delivery of the PBD cytosine (SG3199). The study is currently open and accruing patients with relapsed/refractory ALL.

Phase Ib, open-label, dose escalation and expansion study evaluating the safety and efficacy of entospletinib (GS-9737) with vincristine and dexamethasone in adult with relapsed or refractory ALL. This study is open for previously treated ALL including T-ALL, pre-B ALL and Philadelphia chromosome-positive ALL. Patients with Burkitt leukemia are excluded.

**CONCLUSION**

The Leukemia Department welcomes and will facilitate referrals, and would like to work with you to make novel therapies available to your patients. For referrals, please contact Elias Jabbour, Hagop Kantarjian, or any of the Leukemia faculty listed.

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**Leukemia SERVICE ATTENDINGS**

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</tr>
</tbody>
</table>
1. Newly Diagnosed
A. Acute Promyelocytic Leukemia: cytogenetic feature t(15;17): ATRA + Arsenic +/- Gemtuzumab (2010-0981)
B. Cytogenetic features t(8;21): Fludarabine +/- Ara-C + Idarubicin (2007-0147)
C. Younger Patients:
   - CIA vs FAB (2010-0788)
   - Cladribine + IA + Sorafenib (2012-0648)
   - Nivolumab + IA (2014-0077)
D. Older Patients:
   - Omacetaxine + Decitabine (2012-0312)
   - SG1-110 (2013-0843)
   - Cladribine + LD Ara-C/DAC (2011-0987)
   - DAC 3 vs 10days (2012-1037)
   - Sorafenib + Ara (2014-0576)
   - Ruxolitinib + Decitabine (2014-0344)
   - CPX-351 (2014-0548)
   - Lintuzumab + Nivolumab + Ata (2014-0354)
   - Brutinib +/- Ara-C (2014-0509)
   - SG1-110 vs Treatment Choice (2014-1051)
   - DAC +/- JNI-562247 (2015-0520)
   - AZ-221 vs SOC (2015-0781)
   - IDH1 + Ara (2015-1056)
   - Inotecan + DAC (2016-0198)
E. Mixed Phenotypes:
   - Cladribine + Idarubicin + Ara-C + Vincristine (2013-0703)

2. Salvage Programs
A. AC220 + Ara or Ara-C (2012-1047)
B. DAC + CIA (2012-1064)
C. Omacetaxine (2013-0707)
D. SG1-110 (2013-0901)
F. AC220 vs Salvage Therapy (2014-0344)
G. Ruxolitinib + Dec (2014-0344)
H. Dec + CIA +/- All + SCT (2014-0358)
I. BVD-523 (2014-0391)
J. ABT-199 + Ara or DAC (2014-0690)
K. SGN-CD33A (2014-0744)
L. BCRP324 (2014-0765)
M. EZ201 (2014-0777)
N. Nivolumab + Ata (2014-0863)
O. Lintuzumab + Ara (2014-8662)
P. AG-120 (2014-0800)
Q. Selinexor + Sorafenib (2014-0973)
R. FLX132 (2014-1002)
S. IDH1/305 (2014-1020)
T. CC-886 (2015-0506)
U. IA or Ara + Crizotinib (2015-2070)
V. AMG530 (2015-2096)
W. Rigosertib (2015-3060)
X. INCB05914 (2015-0542)
Y. LY3212942 + IA (2015-0436)
Z. AS2125 vs. Salvage (2015-0604)
AA. LY2663686 + FA (2015-0665)
AB. Abocidib + Ara-C + Mitox (2015-0719)
AC. AG-120 or AG-221 (2015-0702)
AD. IMGN129 (2015-2024)
AE. Cotalexanib or Idaximunib + Venetoclax (2015-0898)
AF. Ara + SGN-CD33A (2015-0884)
AG. AGS027 (2015-1129)
AH. FT-202 (2016-0150)
AI. XmAB (2016-0165)
AJ. MD-8628 (2016-0199)

3. Low Risk MDS and CMML with <10% Blasts
- Bone ATG (2012-0348)
- Oral Ata vs Best Supportive Care (2012-0733)
- Ruxolitinib (2013-03012)
- MED 476 (2013-0414)
- FF-1305(41) (2014-0304)
- ASTX 727 (2014-0508)
- DAC vs Ata (2014-0113)
- OPN-305 (2014-0323)
- Nivolumab + Imatinib + Ata (2014-0939)
- IDH1/305 (2014-1006)
- BL-8040 (2015-0426)
- Arzoxelumab +/- Ata (2015-0257)
- Lupinertcept vs Placebo (2015-0579)

4. MDS/MPN
- Ruxolitinib + Ata (2012-0737)
- Rusertib (2014-0764)

5. Maintenance/MRD
- Lenalidomide (2014-0166)
- SCN-CD33A (2014-0744)
- SL-401 (2014-0863)
- Nivolumab (2015-0213)

Myeloproliferative Disorders
1. Myelofibrosis
   - Soractecept (2012-0514)
   - Ruxolitinib + Ata (2012-0737)
   - PRM-151 (2013-0251)
   - LCL-161 (2014-0012)
   - Monoclonalin (2014-0545/2015-0557)
   - Ruxolitinib + Plerixafor (2014-0445)
   - Nivolumab (2014-0962)
   - SL-401 (2014-0576)
   - Vismodegib + Ruxolitinib (2015-0874)

2. Systemic Mastocytosis
- Brustuzumabina (2012-0714)
- Cren/aCMF
- Ruxolitinib (2014-0764)

CML Treatment Priorities
1. Early Chronic Phase
   - Dasatinib (2015-1043)

2. TKI Failures, T315I Mutations or Advanced Phases
   - Dasatinib + DAC (2011-0333)
   - Cladribine + IA + Sorafenib + TKI (2012-0489)
   - Ponatinib (2015-0212)
   - Omacetaxine (2014-0259)
   - Nilotinib + MEK162 (2014-0312)
   - Dasatinib + Nilotinib (2015-0265)

3. Minimal Residual Disease
- Ruxolitinib (2012-0697)

ALL Treatment Priorities
1. Newly Diagnosed or Primary Refractory (one non-hyperCVAD induction)
   - Age <30, Augmented BFM + Otumaxumab (2014-0788)
   - Age >35: Hyper CVAD + Blinatumomab (2014-0845)
   - Age >60: Low dose Hyper CVAD + CMG-544 (2014-1099)
   - Hyper CVAD + Otumaxumab (2014-0270)
   - Hyper CVAD + Liposomal Vinorelbine (2008-0598)
   - T-cell: Hyper CVAD + Nelarabine (2006-0328)
   - PB: Hyper CVAD + Portaxtinib (2014-0303)
   - PB: Mini-Hyper CVAD + Portaxtinib (2016-0402)
   - Burkitt: EPOCH + Otumaxumab (2014-0213)

2. Salvage Programs
- Low Dose Hyper CVAD + CMG-544 (2010-0993)
- DAC + CIA (2012-0164)
- EPOCH + Otumaxumab (2014-0213)
- Ruxolitinib or Dasatinib + Hyper CVAD (2014-0521)
- LY3094789 + Dec (2015-0208)
- ICA1051805 (2015-0407)
- Dasatinib or Ibrutinib + Hyper CVAD (2015-0529)
- Portaxtinib + Ibrutinib (2014-0763)
- APPO:251 (2014-0528)
- DS-3032B (2014-0569)
- ONC-201 (2014-0731)
- ABL001 (2014-1019)
- AG881 (2015-0534)
- FT-2101 (2015-0516)
- BIL6/25 (2015-0831)
- ADCT-301 (2015-0608)

3. Minimal Residual Disease
- Blinatumomab (2014-0844)