

Acute Lymphoblastic Leukemia in Adults

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Guideline Questions

1. How are adult patients with ALL diagnosed and worked-up?
2. What are the classifications and prognostications of adult ALL?
3. What are the recommended treatment approaches to ALL?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published using the search term 'Acute Lymphoblastic Leukemia'. Clinical trials, clinical practice guidelines, systematic reviews and meta analyses written in English were included.

Target Population

The following recommendations apply to adult cancer patients with suspicion or diagnosis of ALL.

Summary of Recommendations

Diagnosis and Work-up

1. All patients suspected of leukemia should undergo bone marrow studies incorporating morphological assessment, immunophenotyping, cytogenetic +/- FISH and molecular evaluation.
 - a. For B-cell ALL, results of BCR-ABL by PCR or t(9;22) by cytogenetics/FISH should be available within 5 days as this will influence the induction treatment regimen used.
 - b. Patients with failed cytogenetics for B-cell ALL should have molecular/FISH testing for BCR-ABL (if not yet done) and MLL (KMT2A) rearrangement.
 - c. A diagnostic baseline lumbar puncture should be performed with cell count and morphologic evaluation of the CSF cytospin preparation. If the result is unclear, flow cytometry should be performed.
2. If bone marrow studies are not feasible peripheral blood should be sent for immunophenotyping, cytogenetics and molecular studies.
3. Patients for whom anthracycline based treatment is contemplated should receive a cardiac evaluation e.g. MUGA scan or echocardiogram or cardiac MRI.
4. Transplant – eligible patients and their siblings should be HLA typed.

Classification and Prognostication

1. Patients should be classified as having B-cell or T-cell ALL based upon immunophenotyping results.
2. Pre-treatment risk stratification should be ascertained for all patients using age and cytogenetics/FISH and/or molecular studies.
3. Post-treatment risk stratification should include the outcomes of measurable residual disease (MRD) assessment using either flow cytometry or molecular techniques (see below)

4. Although genetic profiling is not routinely done, certain patients should be tested for the presence of a TP53 mutation by NGS, e.g. those with low hypodiploidy.

Principles of Treatment Initiation

1. Induction therapy should only be administered in a leukemia centre with physician and nursing expertise in the management of acute leukemias.
2. Induction therapy should not be initiated until the BCR-ABL status is known. If the patient is symptomatic, a steroid pre-phase should be initiated.
3. Initiation of induction therapy should be accompanied by tumour lysis syndrome (TLS) prophylaxis, including hydration, urate lowering agents and close monitoring of TLS chemistries.

Treatment of Ph/BCR-ABL negative ALL

1. Eligible adults under age 55-60 should be treated with a pediatric-based protocol.
 - a. In Alberta the current standard regimen is the modified Dana Farber Cancer Institute (DFCI) Canadian Leukemia Study Group (CLSG) protocol.
 - b. Patients with co-morbidities, or those unable to tolerate the full DFCI protocol, may be treated with a less intensive regimen, such as the modified DFCI protocol for patients age 60 or over.
2. Fit adults age 55-75 should be treated with curative intent.
 - a. The Princess Margaret Hospital modified DFCI protocol for adults above age 60 has produced favourable results in this population compared to other regimens and may be used. Other curative-intent regimens are also acceptable.
3. All patients with B-ALL who are in complete remission should receive blinatumomab as part of post-remission therapy, regardless of MRD status. Patients not proceeding to early allogeneic HSCT should receive 4 cycles of blinatumomab.
4. Patients over age 75, or those under age 75 with major co-morbidities precluding intensive chemotherapy, should be considered for palliative chemotherapy with corticosteroids and vincristine +/- low-dose asparaginase, followed by low-dose maintenance chemotherapy if CR is achieved. The PETHEMA (Ribera) protocol may be used for such patients.
5. BCR-ABL negative patients should have bone marrow MRD assessment by flow cytometry following induction chemotherapy, and repeated post-blinatumomab if positive at the end of induction. If MRD by flow cytometry was positive post-induction and negative or indeterminate post-blinatumomab, molecular IgR MRD detection (e.g. ClonoSEQ^R) should be performed.
 - a. If not proceeding to HSCT, periodic monitoring of bone marrow MRD status should be performed during post-remission therapy and at the end of treatment.
 - b. B-ALL patients with persistent MRD positivity by flow cytometry and/or IgR (ClonoSEQ) after induction plus one cycle of Blinatumomab, or those with later recurrence of detectable MRD, should be considered for allogeneic HSCT in CR1, as these patients are at higher risk of relapse. If MRD is negative post-blinatumomab, HSCT is not indicated unless high risk genetic features are present (see below).

- c. T-ALL patients who are MRD positive post-induction should receive intensified chemotherapy with an intent to achieve MRD negativity. These patients should be referred for HSCT if otherwise eligible.

Treatment of Ph/BCR-ABL positive ALL

1. Ph/BCR-ABL positive patients who are fit for chemotherapy should be treated with a BCR-ABL tyrosine kinase inhibitor (TKI) combined with induction and post-remission therapy.
 - a. A less intensive induction regimen with corticosteroids, vincristine and TKI (e.g. Chalandon protocol) is preferred over intensive chemotherapy for initial induction, as it produces higher CR rates due to lower induction mortality. In younger, fit patients, this should be followed by intensification (e.g. HyperCVAD Part B + TKI, as per the Chalandon protocol).
 - b. Patients achieving a hematologic CR should be continued on post-remission chemotherapy + TKI. This may consist of the modified Princess Margaret Hospital DFCl CNS, intensification and maintenance phases, or HyperCVAD + TKI. Asparaginase should not be used due to increased toxicity when used concurrently with TKI.
 - c. Imatinib (600 – 800 mg per day) or dasatinib (100 mg daily) may be used as the first line TKI agent.
 - i. Patients with intolerance to, or not achieving an adequate response to, imatinib should be switched to a second generation TKI such as dasatinib, or ponatinib.
 - ii. Ponatinib should be used in patients with a T315I mutation, or in those with evidence of persistent disease using a second generation TKI.
 - iii. For patients with CNS disease at diagnosis, dasatinib should be used upfront due to its superior CNS penetration.
 - d. Patients with Ph/BCR-ABL positive ALL who are elderly, or otherwise unfit for intensive chemotherapy or transplant, should be treated with the Chalandon induction protocol cycle A, or corticosteroids + TKI, followed by low-dose maintenance chemotherapy + TKI.
 - e. Patients should have MRD assessments following induction chemotherapy, by quantitative *BCR-ABL* PCR and by bone marrow flow cytometry. If MRD detection by flow cytometry is inadequate or indeterminate, molecular IgR MRD detection (e.g. ClonoSEQ^R) should be performed.
 - g. Patients who are MRD positive by flow cytometry post-induction should be treated with at least one cycle of blinatumomab, with an aim to achieve MRD negativity by flow. If flow and/or IgR remains positive, patients should be referred for HSCT.
 - f. If unable to tolerate post-remission chemotherapy, or are MRD positive by flow or IgR post-Blina x1 and are not proceeding to HSCT, blinatumomab x 5 cycles + TKI should be considered.
 - g. Patients who are MRD positive by PCR at the end of a two-cycle induction using the Chalandon protocol with imatinib, or by week 16 using other protocols, should be switched to a second generation TKI such as dasatinib. If already on a 2nd generation TKI, the patient may be switched to ponatinib. The TKI should be combined with either chemotherapy or blinatumomab.

- h. TKIs should be continued indefinitely in patients who are not transplanted.
- i. Patients not transplanted should be closely monitored for disease progression with serial PCR testing of peripheral blood or bone marrow every 3 months. Patients with reappearance of PCR positivity or rise in transcript levels should have a repeat bone marrow for flow MRD +/- IgR (ClonoSEQ^R). Patients with reappearance of MRD positivity by these techniques should be referred for HSCT (see below).
- i. Patients with a major increase in, or reappearance of, *BCR-ABL* transcripts by PCR, should have mutational testing, specifically to look for the presence of a T315I mutation.

Role of allogeneic stem cell transplantation (HSCT)

1. Allogeneic HSCT should not be routinely performed in patients with Ph/BCR-ABL negative ALL in CR-1. However, patients up to age 75 with the following high-risk features should be considered for HSCT:
 - i. t(4;11) with MLL (KMT2A) rearrangement, if MRD positive post-induction
 - ii. Low hypodiploid ALL, esp. with TP53 mutation, if MRD positive post-induction
 - iii. Early T-cell precursor (ETP) ALL
 - iv. Other T-ALL, if MRD positive post-induction
 - v. Lack of attainment of hematologic CR with first induction
 - vi. Persistent or recurrent MRD positivity, as outlined above.
 - vii. Inability to deliver sufficient asparaginase dosing during intensification therapy
 - a. There is no clear evidence that other cytogenetic abnormalities, or specific cell surface markers, constitute high risk features when using a pediatric-based regimen
 - b. It is also not clear whether patients with a high-risk feature at baseline who achieve MRD negativity after induction therapy require a transplant. These B-ALL patients may be continued on chemotherapy + blinatumomab.
2. BCR-ABL positive patients up to age 75 should be considered for allogeneic HSCT in CR-1 if the following are present:
 - a. Persistent or recurrent MRD positivity by flow +/- IgR (ClonoSEQ), as outlined above.
 - b. If other high-risk features are present, e.g. IKZF^{plus} genotype, if available.
 - c. Reappearance or major rise in *BCR-ABL* transcript levels
 - d. Persistent stable low-level *BCR-ABL* positivity is not in itself an indication for HSCT, provided bone marrow flow +/- IgR (ClonoSEQ) testing is negative.
3. If an HLA matched related or unrelated donor is unavailable, a haploidentical transplant should be considered.

CNS prophylaxis

1. Intrathecal chemotherapy: All patients should receive intrathecal chemotherapy prophylaxis, starting with the initiation of induction therapy, and continuing through maintenance therapy, for 11-12 total doses.

- a. If the initial CSF is positive, intrathecal chemotherapy should be administered twice weekly until CSF clearance is confirmed on at least 3 occasions.
2. Cranial Radiation: Cranial radiation may be omitted from CNS prophylaxis, unless there is evidence of fixed CNS disease.

Supportive care

1. Antimicrobial prophylaxis against PJP and HSV/VZV should be used from induction through the completion of maintenance therapy. Antifungal prophylaxis should be used during intensive induction therapy.
2. Asparaginase therapy requires close monitoring for liver toxicity, pancreatitis, hypertriglyceridemia and VTE.
 - a. Anticoagulation prophylaxis should be considered during intensification therapy. Documented VTE should be treated with full-dose anticoagulation but asparaginase therapy can generally be resumed after several weeks if stable or improved.
 - b. Asparaginase therapeutic drug monitoring should be routinely performed in all patients during and at the end of the first intensification cycle, at a later cycle and after any dose reduction, targeting a trough level of ≥ 0.1 U/L. Those with undetectable levels early in the cycle, indicating the presence of neutralizing antibodies, should be switched to crisantaspase.
 - c. Dose reductions should be considered for grade 2 or greater hepatic toxicity.
 - d. Pancreatitis requires discontinuation of asparaginase.
3. Prophylaxis against corticosteroid-induced osteoporosis and gastritis should be used.

Relapsed ALL

1. Transplant-eligible BCR-ABL negative B-ALL patients should be treated with an antibody-based regimen, either blinatumomab or inotuzumab (if CD22 positive).
2. CAR-T therapy may also be used in CD19+ B-ALL patients as per below.
3. BCR-ABL positive patients relapsing on an imatinib-based regimen should be treated with a second generation or third generation TKI + either chemotherapy, inotuzumab or blinatumomab. If a T315I mutation is detected, or if relapsing on a second generation TKI, ponatinib plus blinatumomab or chemotherapy should be used.
4. T-ALL patients should receive a non-cross resistant re-induction chemotherapy regimen, or nelarabine.
5. Transplant eligible patients should be considered for allogeneic HSCT in CR-2, if not performed in CR-1.

CAR T-Cell Therapy:

1. Indicated for CD19+ B-ALL patients with one of the following:
 - a. Relapsed after allogeneic HSCT

- b. Refractory to 2 or more treatment regimens, one of which could be antibody-based therapy
 - c. Relapsed/refractory and not considered suitable candidates for or declining HSCT, or used as a bridge to transplant
2. Patients should be referred for apheresis prior to administering salvage immunosuppressive chemotherapy such as corticosteroids or cyclophosphamide, to avoid interfering with the quality of the product.
 3. Patients should in most cases receive bridging/cytoreductive therapy following apheresis, to prevent clinical deterioration due to disease progression and to achieve cytoreduction prior to CAR T infusion. This may consist of either chemotherapy or antibody-based therapy. However, exposure to inotuzumab should be minimized if possible.
 4. Achievement of a hematologic CR, if possible, is preferred prior to undergoing CAR-T therapy, as this results in optimal outcomes and less toxicity.
 5. Allogeneic HSCT post-CAR-T should be considered in younger patients who have not had prior HSCT, esp if not MRD negative, but is generally not needed for patients relapsing post-HSCT. HSCT should also be considered in patients with early loss of CAR-T cells (within 3 months).

A. Background

Acute Lymphoblastic Leukemia (ALL) is a highly aggressive hematologic malignancy resulting from the proliferation and expansion of lymphoid blasts in the blood, bone marrow and other organs.¹ ALL occurs with a bimodal distribution with an early peak in children 4 – 5 years old followed by a second peak at ~ 50 years of age² with the worldwide incidence being ~ 1 – 4.75/100,000 individuals with a male:female prevalence of roughly 1:3:1.¹ It is the most common childhood acute leukemia accounting for ~ 80% of the pediatric leukemias but contributing to only 20% of adult leukemias. Although significant progress has been made in treating adult ALL the overall survival amongst adults 18 to 60 years old is only 35% in contrast to childhood ALL in which overall survival at five years is more than 80%.¹

Over the past two decades the treatment of adult ALL has changed significantly with the introduction of pediatric protocols for the treatment of adolescents and young adults, the addition of tyrosine kinase (TKI) inhibitors for the treatment of Philadelphia positive/BCR-ABL positive ALL, a reevaluation of the role of allogeneic stem cell transplantation for standard risk ALL patients, the incorporation of minimal residual disease into risk assessments and most recently the introduction of novel agents such as blinatumomab, inotuzumab and chimeric antigen receptor – T cell therapy for relapsed/refractory ALL.

Pathogenesis

ALL is thought to arise from interactions between exogenous or endogenous exposures, genetic susceptibility, and chance. Infection was the first suggested causal exposure for childhood acute lymphoblastic leukemia. After the Hiroshima and Nagasaki atomic detonations, ionizing radiation quickly became established as an exposure leading to childhood ALL.³ Chromosomal translocations occurring in utero during fetal hematopoiesis have been suggested as the primary cause for pediatric ALL while postnatal genetic events are considered secondary contributors.^{4, 5} Many of these chromosomal rearrangements disrupt genes that regulate normal haematopoiesis and lymphoid development (e.g. RUNX1, ETV6), activate oncogenes (eg, MYC), or constitutively activate tyrosine kinases (e.g. ABL1). Patients with trisomy 21, Klinefelter's syndrome and inherited diseases with excessive chromosomal fragility such as Fanconi's anemia, Bloom's syndrome and ataxia-telangiectasia have a higher risk of developing ALL.⁶ However, in the majority of ALL patients no gross chromosomal alteration is noted suggesting that additional submicroscopic genetic alterations likely contribute to leukaemogenesis.⁵ Genome-wide association studies of childhood⁵ have noted common allelic variants in IKZF1, ARID5B, CEBPE, and CDKN2A which have been significantly and consistently associated with childhood ALL.⁵ Others have investigated the associations of genetic polymorphisms in folate pathway and DNA repair genes with susceptibility to ALL.⁷ Although several genetic alterations have well established roles in leukemogenesis (e.g. activating mutations in NOTCH1) the roles of many others remains elusive.

Clinical Manifestations, Diagnosis, and Work-up

Clinical manifestations of ALL are highly variable. At presentation patients may have a multitude of constitutional symptoms, easy bruising, bleeding, dyspnea, dizziness, and infections due to anemia, thrombocytopenia and neutropenia. Extremity and joint pain may be the only presenting symptoms in some patients.⁸ Lymphadenopathy, splenomegaly and/or hepatomegaly are seen on physical examination in approximately 20% of patients.⁸ Abdominal masses from gastrointestinal involvement or chin numbness from cranial nerve involvement may be seen but are more suggestive of mature B-ALL. Less than 10% of patients have symptomatic central nervous system (CNS) involvement. T-lineage ALL with a mediastinal mass can cause stridor and wheezing, pericardial effusions, and superior vena cava syndrome. Testicular involvement is rare in adults.⁹

The diagnosis of ALL begins with an evaluation of the peripheral blood film which may identify the presence of blasts. Patients presenting with only a mediastinal mass or lymphadenopathy require a tissue biopsy. All patients should have a bone marrow examination. By convention the term lymphoblastic lymphoma is used when the process is confined to a mass lesion with no or minimal evidence of peripheral blood and bone marrow involvement. Based on morphologic, genetic and immunophenotypic features, lymphoblastic lymphoma is indistinguishable from ALL, and is in fact not distinguished in the WHO 2022 classification.

The assessment of immunophenotype by flow cytometry is essential to establishing the diagnosis.⁹ The initial immunophenotyping panel should be comprehensive enough to establish a leukemia associated phenotype (LAP) to allow for use in minimal disease monitoring (MRD). Cytogenetic examination with examination of metaphases is standard, and fluorescence in situ hybridization (FISH) is crucial (e.g, for BCR-ABL and MLL-AF4) particularly in cases in which cytogenetics are unavailable or have failed. Screening by polymerase chain reaction (PCR) for the BCR-ABL transcripts is also essential as it significantly impacts treatment. Determination of the BCR-ABL breakpoint is also required for subsequent molecular monitoring. Some labs also evaluate blast cells with molecular methods for the detection of patient-specific immunoglobulin and T-cell receptor (Ig/TCR) rearrangements⁹; however, this is not routinely performed within Alberta. If bone marrow transplant is a consideration, tissue typing of both the patient and siblings should also be performed at diagnosis. If there are no HLA-matched siblings, consideration should be given to prompt initiation of an unrelated donor search.

Recommendations:

The initial work-up of patients with ALL should include a thorough history and physical examination as well as baseline laboratory investigations including complete blood count, chemistry with extended electrolytes, tests of renal and liver function including amylase and lipase, a disseminated intravascular coagulation panel, and a tumour lysis panel. Cardiac imaging e.g. echocardiogram, multigated acquisition (MUGA) scan or cardiac MRI should be undertaken for all patients due to the use of anthracyclines.

Bone marrow studies or peripheral blood studies incorporating, as noted above, immunophenotyping, cytogenetics, and molecular studies should be completed. Ideally results of BCR-ABL testing should be available prior to the initiation of induction therapy, and should be available within 5 days. Lastly, patients eligible for allogeneic stem cell transplantation, and their siblings should have human leukocyte antigen (HLA) typing performed.

B. Classification and Prognostication

Classification of ALL:

The WHO 2016 classification is largely based on recurrent cytogenetic abnormalities, but also includes molecular markers such as KMT2A and BCR-ABL (Table 1). There is also a new provisional entity encompassing the BCR-ABL-like genotype (described later), which is not to this point readily diagnosed using routine testing. B-lymphoblastic leukemia/lymphoma NOS encompasses all subtypes not otherwise defined by one of the recognized abnormalities.

It is notable that this classification does not primarily distinguish between different immunophenotypic features, apart from the provisional T cell entities. It also does not distinguish between T-lymphoblastic lymphoma and T-ALL, acknowledging the widely held view that these are different clinical presentations of the same disease, and should be managed similarly. On the other hand, early T-cell precursor (ETP) lymphoblastic leukemia has been identified as a distinct subtype with unique biologic and clinical characteristics.

Table 1: WHO (2016) classification of ALL¹⁰

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);KMT2A rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor (ETP) lymphoblastic leukemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Prognostic Factors in ALL:

Prognostic models for ALL have been refined continuously with improvements in therapy rendering some prognostic variables invalid.⁹ The following represent clinical, cytogenetic and important molecular risk factors. It is important to note that many of these factors were defined using adult – based protocols and more studies are needed to evaluate their significance with pediatric based protocols.

Clinical Prognostic Factors:

Age, Gender and Ethnicity

Age is an important prognostic factor in ALL. In children age (infant or ≥ 10 years old) is an unfavourable risk group especially those younger than 6 months old.^{5,17} Regardless of the treatment protocol utilized older adults are regarded as a prognostically unfavorable group. One study noted that the outcomes of patients aged over 55 had a probability of survival of 20% at 3 years while others have noted that patients over the age of 35 have poorer outcomes.¹¹⁻¹⁵ Recent data suggest that adolescents and young adults benefit with improved overall survival if treated according to pediatric protocols.¹ Several studies have suggested that the influence of age may relate to the increased prevalence of poor-risk features while others have suggested that it is independent of cytogenetic and molecular aberrations.^{16, 17} The ability to tolerate chemotherapy likely plays an important role.^{13, 18, 19} Together with age, male gender and race (Hispanic or of African descent) have been considered negative prognostic factors in pediatric ALL Inaba, 2013 #20. Racial differences in prognosis have been linked to socioeconomic factors but also to differences in genomic variations. For example, germline single nucleotide polymorphisms of PDE4B and ARID5B are associated with Native American genetic ancestry and somatic CRLF2 were over-represented in children with a Hispanic background.

White Blood Cell Count

In children, a presenting leucocyte count ($\geq 50 \times 10^9/L$) has been associated with a worse prognosis.¹⁷ In many, but not all adult studies of ALL, high-risk ALL has been defined as WBC $\geq 30 \times 10^9/L$ for B-cell ALL and $\geq 100 \times 10^9/L$ for T-cell ALL.^{1, 11, 13-15} Although most early studies identifying this factor used adult-based protocols, subgroup analyses in larger studies show that these continue to be important prognostic factors with pediatric-inspired regimens Brandwein, 2011 #51; Boissel, 2003 #357. In their study of the DFCI protocol in adults a high WBC ($>30 \times 10^9/L$ for Pre-B ALL or $>100 \times 10^9/L$ for T-ALL) was associated with inferior RFS and OS.²⁰ However, subsequent studies incorporating early MRD detection into multivariate models have demonstrated that baseline WBC was no longer an independent predictor of relapse (see section on MRD).²¹

Immunophenotype

The SEER database demonstrated a better prognosis with B cell as compared with T cell immunophenotype in patients < 20 years; while in patients ≥ 20 years of age, T cell

immunophenotype was more favorable.²² This was confirmed in a metanalysis by Kako et al. of published studies from January 1998 to March 2013 to compare the outcomes of chemotherapy for T- and B- lineage ALL and noted superior survival in patients with T-lineage ALL compared to those with B-lineage ALL although the inclusion of patients with Ph+ ALL likely influenced the.²³

Amongst adults T-cell ALL accounts for 14–22% of adult ALL²⁴ and is thought to be of favourable prognosis. In both the LALA 87 and the UKALL/EGOG 2993 trial, T-ALL was associated with male gender, age <35 - 39 years old, CNS involvement and a high WBC count. The LALA-87 investigators also noted a higher incidence of a mediastinal mass and anemia.^{15, 24} In this study for patients age <40 treated with chemotherapy alone 3 year DFS was superior in the group with a T-cell phenotype relative to a B-ALL phenotype (59% vs. 20%). No difference in DFS was seen in patients with B- or T-ALL patients treated with allo- or auto – HSCT.²⁴ Similarly, Both Rowe et al. and Larson et al. noted that improved OS in patients with T-cell antigen expression relative to B-lineage antigens.^{13, 18} Kantarjian et al. using Hyper-CVAD noted similar results.¹² Using the pediatric Dana Farber Cancer Institute (DFCI) protocol a trend toward improved clinical outcomes was observed in adolescents²⁵ and adults^{20, 26} with T-ALL. The GRAALL study group⁹⁴ noted that when using a pediatric protocol at 42 months, EFS was estimated to be 62% (95% CI, 50% to 72%) in T-ALL patients and 52% (95% CI, 42% to 59%) in BCP-ALL patients (p=0.09). Within the T-cell ALL subset the prognosis is worse for pro-, pre- and mature-T subtypes (CD1a-, CD3-/CD3+) compared with the CD1a+ cortical/thymic phenotype. The early T-cell precursor ALL which retains stem cell-like features is associated with a dismal prognosis with conventional chemotherapy²⁷ in both adult and pediatric T-ALL.²⁸

Patients with a CD10-negative pro-B phenotype are considered as high-risk particularly when associated with t(4;11)/abn q23, with KMT2A rearrangement.^{1, 26} The CD20 antigen is expressed in nearly half of B-cell ALL and its impact on clinical outcomes is controversial. The pediatric GRAALL 2003 protocol in adults aged 15-60 years old with Ph-negative ALL reported that CD 20 expression did not influence achievement of complete remission but was associated with a higher cumulative incidence of relapse (CIR) and lower EFS at 42 months (42% vs. 29%) in patients with a WBC $\geq 30 \times 10^9/L$ (P=0.006). Thomas et al. also noted an inferior survival in CD20 positive patients using the adult-based hyper-CVAD protocol.²⁹ In contrast, a retrospective analysis by the Princess Margaret Hospital in adult patients, most of whom had received a pediatric-based regimen, did not find any association between CD20 expression and outcome³⁰ and in-fact there appeared to be a trend towards a favourable EFS in those showing CD20 positivity.

Cytogenetic Factors

Karyotype is an important prognostic factor with a number of cytogenetic abnormalities being associated with altered prognosis in ALL (Table 2). The frequency of cytogenetic aberrations varies between adult and childhood ALL and may partially explain the differences in clinical outcomes between patient populations.⁸ Whether cytogenetic abnormalities remains important with the use of pediatric protocols in adult patients remains unclear; some studies suggest that most abnormalities

are not independent predictors of outcome in adults treated with such protocols, with the exception of KMT2A-associated abnormalities.^{20, 21, 26}

The Philadelphia chromosome, characterized by the t(9;22) translocation resulting in production of a BCR-ABL1 fusion gene and protein, is the most common cytogenetic and molecular abnormality in adult ALL. The frequency is age-dependent, being present in approximately 8–10% of adolescents, 15-30% of younger and middle aged adults, and 40-50% of elderly ALL patients.⁹ Over two-thirds have the p190 gene, with the remaining harbouring the p185 gene. Until recently the BCR-ABL1 fusion gene marked the most unfavourable subgroup of adult ALL. With chemotherapy alone the CR rate was 75%- 80%, median DFS about 10 months and 5-year survival below 10-20%.^{26, 31, 32} Most studies demonstrated superior outcomes with allogeneic HSCT compared to chemotherapy alone.^{26, 31, 32} Combinations of tyrosine kinase inhibitors (TKIs) with chemotherapy have produced superior outcomes to chemotherapy alone, as will be discussed later.

The t(4;11) is present in up to 60 % of infants younger than 12 months but is uncommon in adult patients, constituting 5-10% of cases. When rearranged, the MLL (now called KMT2A) gene has been found to be associated with inferior RFS and OS in adult patients when using a pediatric protocol.²⁰ The t(1;19) is uncommon in adults; its prognostic significance is unclear, with conflicting data. Garg et al. noted that adults treated with Hyper CVAD had a significantly better CRD and OS compared with all other patients.³³ However, Foa et al. found that this abnormality is frequently associated with early treatment failure, and recommended that these patients should be considered for intensified treatment strategies.³⁴ The t(12;21) abnormality leading to *ETV6-RUNX1* fusion is detectable in about 25 % of children and 3 % of adults with B-ALL. Patients generally have a favorable prognosis.^{35, 36}

Hyperdiploidy (>50 chromosomes) is seen in approximately 25% - 30% of paediatric cases and 7% of adults and represents the most common chromosomal abnormality in children. It is associated with a favourable prognosis regardless of age and leukocyte count at presentation.^{37, 38} Its characteristic genetic feature is the nonrandom gain of chromosomes X, 4, 6, 10, 14, 17, 18 and 21, with individual trisomies or tetrasomies being seen in over 75% of cases. The individual structural abnormalities do not appear to influence outcome in patients with hyperdiploidy except for the t(9;22), which is associated with a poor prognosis.³⁹ The favourable prognosis may reflect an increased propensity of these cells to undergo apoptosis.¹⁷ In contrast, 5 % to 6 % of ALL patients, independent of age, have the loss of various chromosomes, resulting in a hypodiploid clone with fewer than 44 – 46 chromosomes. These patients generally have a poor prognosis, especially those with near-haploid and low-hypodiploid clones.^{17, 36, 40} Recent data suggest that complex karyotypes (≥ five chromosomal abnormalities) occur more frequently with increasing age and may be associated with inferior survival.^{15, 26, 41}

Intrachromosomal amplification of chromosome 21 (iAMP21) occurs at an incidence up to 2 % in older children with B-cell precursor ALL Harrison, 2005 #1056 and is defined by at least three copies of the RUNX1 gene (Children's Oncology Group, COG, definition for iAMP21). iAMP21 has been shown to be linked to a dismal outcome when patients are treated with standard therapy, because it is associated with an increased risk of both early and late relapses.^{36, 42-44} It is rare in adults.

Some studies have identified low hypodiploidy as an adverse prognostic factor in B-ALL; it has been associated with *TP53* mutations in about 90% of cases^{169,170}; however, other studies have not found it to be predictive using pediatric inspired regimens²¹. Low hypodiploidy is also associated with inferior outcomes with chemotherapy + blinatumomab.¹⁵⁸

Many of these prognostic factors may be regimen dependent. Many older studies used adult-based protocol. In contrast, using pediatric based regimens, most of these cytogenetic abnormalities have not been found to be of prognostic importance in adults, with the notable exception of t(4;11).⁴⁵⁻⁴⁷

Molecular Genetic Factors

Molecular genetics has identified several gene mutations, translocations and amplifications that may have prognostic significance in ALL. IKZF1 encodes IKAROS which has been established as one of the most clinically relevant tumor suppressors in ALL. It is a DNA-binding zinc finger transcription factor that regulates the development and function of the immune system and acts as a master regulator of normal hematopoietic differentiation and proliferation, particularly in lymphoid lineage.⁴⁸ Deletion of a single IKZF1 allele or mutations of a single copy of IKZF1 were first detected in 15 % of pediatric B-cell ALL and in more than 80 % of Ph+ ALL cases, either de novo Ph+ ALL or chronic myeloid leukemia at progression to lymphoid blast crisis suggesting a critical role in the pathogenesis of Ph+ ALL.⁴⁹⁻⁵² The incidence in adults is about 50% in B-cell ALL and about 65% when *BCR-ABL* positive. PAX5 encodes a transcription factor known as B-cell specific activator protein, that plays a key role in B-cell commitment by activating essential components of the B-cell receptor signaling and repressing the transcription of genes necessary for T-lymphopoiesis.⁵³ Monoallelic deletion of PAX5 have been observed in about 30 % of children and adults^{54, 55} and have been demonstrated to not influence treatment outcome.^{36, 55, 56} The CDKN2A/B locus encodes for the INK4-class cyclin dependent kinase inhibitors p15INK4B, p16INK4A and for p14ARF. CDKN2A and CDKN2B deletions have been identified in 29 % and 25 % of *BCR-ABL1*-positive ALL patients, respectively.⁵⁷

Recent data further suggest that together with Ph+ve ALL, mutations in IKZF1 are also a hallmark of '*BCR-ABL1*-like ALL'.⁵ Alteration of the IKAROS gene is associated with increased risk of treatment failure and relapse in both *BCR-ABL1*-positive and *BCR-ABL1*-negative disease independent of commonly used risk stratification features such as age, sex, white cell count, and levels of minimal residual disease (MRD).^{21, 52} More recently, an IKZF1^{Plus} genotype (IKZF + PAX5 or CDKN2A/B

deletions) has been identified as a high risk feature for relapse in *BCR-ABL* positive B-ALL, especially when associated with kinase domain mutations.¹⁷¹

Four independent groups in late 2009 and early 2010 identified that up to 50% of *BCR-ABL* 1-like ALL cases have dysregulated expression of CRLF2, the gene encoding the cytokine receptor-like 2 factor.^{56, 59-61} Overall aberrant expression of CRLF2 was found in 12.5 % to 15 % of B-ALL that lacks typical chromosomal rearrangements and in 50–60 % of Down Syndrome (DS) associated ALL, suggesting that CRLF2 overexpression is especially relevant to tumorigenesis in patients with trisomy 21 Mullighan, 2009 #1021; Hertzberg, 2010 #1030; Yoda, 2010 #1031. Patients with CRLF2 rearrangements had extremely poor treatment outcomes compared with those without CRLF2 rearrangements (35.3% vs 71.3% relapse-free survival at 4 years).⁶²

Mutations of NOTCH1, a transmembrane receptor-encoding gene that regulates normal T-cell development, have been detected in about 60% of T-ALL.⁶³ Early studies in paediatric T-ALL showed that NOTCH1 mutations may be associated with a favourable prognosis.^{21, 63-68} Similarly, in adult T-ALL patients, studies have demonstrated a better prognosis for patients with NOTCH1 and/or FBXW7 mutations,^{67, 69} but this could not be validated in a series of 88 patients treated in the MRC UKALLXII/ECOG E2993 protocol⁷⁰ or by the Zhu et al who in fact noted that Chinese adult TALL patients with mutated NOTCH1 had poorer survival compared with those with wild-type NOTCH1.⁷¹ Overall these studies seem to suggest that NOTCH activation is associated with improved early therapeutic response. However, this early benefit translates into improved overall survival only in some series, probably due to differences in therapy.⁶³

BCR-ABL like ALL

Mullighan and colleagues identified some patients with Ph-negative ALL which had a gene expression profile almost identical to Ph+ ALL and which were termed Ph-like ALL.^{54, 56, 72} This gene-signature has been noted in approximately 15% of pediatric cases, but the frequency is as high as 33% in adults with B-ALL.⁷³ Genetic alterations of activating kinases or cytokine receptor signaling, including ABL, JAK2, CSF1 and EPOR, are commonly observed in addition to overexpression of cytokine receptor-like factor 2 (CRLF2) and frequent deletions of *IKZF1*.^{54, 56, 72, 74} Some studies have found higher levels of MRD after induction therapy,^{74, 75} increased relapse rates and inferior overall survival.⁸ However, reliable testing for this genotype is not routinely available in most laboratories, including in Alberta.

Early T-cell precursor acute lymphoblastic leukaemia (ETP – ALL)

ETP – ALL accounts for 12% of paediatric T-ALL. It is an aggressive leukaemia characterised by an immature immunophenotype with lack of CD1a and CD8 expression, weak CD5 expression⁷⁶ and aberrant expression of myeloid and stem cell markers (CD117, CD34, HLA-DR, CD13, CD33, CD11b, or CD65) on at least 25% of lymphoblasts.⁸ The long-term response to therapy is one of the worst among recognized high-risk forms of childhood ALL.²⁷ In one study, the 10 year OS was 19%

compared with 84% in the non-ETP ALL.²⁷ Similarly inferior outcomes have been reported in adults with ETP-ALL.^{77, 78} The mutational spectrum in ETP-ALL is similar to myeloid tumours with a high frequency of activating mutations in the cytokine receptor and RAS signaling pathways including NRAS, KRAS, FLT3, IL7R, JAK3, JAK1, SH2B3, and BRAF, raising the possibility that addition of myeloid-directed therapies might improve the outcome of ETP ALL.⁷⁹ Given the poor outcomes with conventional ALL regimens, most ETP-ALL patients are referred for allogeneic HSCT in CR1, where there are data suggesting a survival benefit.⁷⁸

Other Prognostic Factors:

Pharmacogenetics and pharmacogenomics

Genome-wide analyses have identified specific gene signatures which may be prognostically relevant when associated with drug resistance e.g. polymorphism of genes metabolizing thiopurines, methotrexate, and cytarabine all of which have been associated with variable treatment response and are a mechanisms of drug resistance.¹ Rocha et al noted that the glutathioneS-transferasel1(GSTM1) non-null genotype was associated with a higher risk of recurrence, which was increased further by the thymidylate synthetase (TYMS) 3/3 genotype. Others have observed that hyperdiploid cells accumulate more methotrexate polyglutamates as they possess extra copies of the gene encoding reduced folate carrier, an active transporter of methotrexate. Hareedy et al found significant associations between variants in genes coding for enzymes and transporters related to the 6-mercaptopurine pathway and clinical outcomes as well as hematological toxicity (neutropenia, agranulocytosis and leukopenia) in pediatric patients with acute lymphoblastic leukemia.⁸⁰ The membrane transporter P-glycoprotein, encoded by the ABCB1 gene, influences the pharmacokinetics of anti-cancer drugs. Gregers et al. noted statistically significant association between ABCB1 polymorphisms, efficacy and toxicity in the treatment of ALL.⁸¹

Table 2: Prognostic Factors in ALL

Abnormality	Clinical Impact	Notes
Cyto-Genetics		
Philadelphia Chromosome	Poor prognostic indicator	8-10% of adolescents. 15-30% adults. 50% elderly.
KMT2A Rearrangements	Poor prognostic indicator	Significance in adult patients using paediatric protocols? Immature immunophenotype, B-cell lineage, co-expression of myeloid antigens and high leukocyte counts.
t(1;19) [TCF3-PBX1]	Variable	30% of childhood ALL; Adverse prognosis can be overcome with intensive chemotherapy in adults and children, increased risk of CNS relapse Jeha, 2009 #190.

Abnormality	Clinical Impact	Notes
t(12;21)[ETV6- RUNX 1]	Favourable prognosis	Adults treated with Hyper CVAD had better CRD and OS compared with all other patients Garg, 2009 #861.
iAMP of chromosome 21	Poor prognosis	Detectable in about 18-25% of children and 1-3% of adults.
Hyperdiploidy	Favourable prognosis	2% of older children with B-ALL.
Hypodiploidy	Poor prognosis	25-30% of cases; nonrandom gain of chromosomes X, 4, 6, 10, 14, 17, 18 and 21; The favourable prognosis may reflect an increased propensity of these cells to undergo apoptosis.
Complex Karyotype	Poor prognosis	5-6% of ALL patients; near haploid and low-hypodiploid have the worst prognosis.
		More than 5 chromosomal abnormalities.
Molecular Genetics		
IKZF1 mutations	Poor prognosis	Most commonly present in BCR-ABL + ALL or BCR-ABL like ALL.
PAX5	No effect on treatment outcomes	30% of adults and paediatric patients.
CDKN2A/B	Prognosis uncertain	CDKN2A – 29% of BCR-ABL positive patients CDKN2B – 25% of BCR-ABL positive patients
CRLF2	Extremely poor outcomes.	12.5% - 15% of B-ALL in patients lacking typical rearrangements; 50-60% down syndrome ALL.
NOTCH	Improved prognosis	50% concomitant mutations in JAK 1/2. Most common alteration in T-ALL; 60% of T-ALL Maybe associated with FBXW7 mutations – which may worsen survival.
Molecular Profiling		
BCR-ABL Like ALL	Poor prognosis	15% of B-cell ALL. May be responsive to treatment intensity
Early T-cell phenotype	Poor Prognosis	Distinct gene-expression profile. Lack of CD1a, CD8 and weak CD5 expression. Long-term response to therapy one of the worst in childhood ALL.
Other Prognostic Factors		
Epigenetics	Unknown prognostic significance	Up to 80% of patients; Unclear clinical implications. T-ALL expressing EZH2 had a lower probability of DFS compared to T-ALL negative for EZH2

Abnormality	Clinical Impact	Notes
Pharmacogenomics		Determine response to drugs and toxicities of ALL therapy. GlutathioneS-transferase 1 phenotype associated with higher risk of recurrence. Hyperdiploid cells accumulate more MTX and have increased toxicity. Variants in genes encoding enzymes and transporters related to the 6-MP pathways influence toxicity. Variants of ABCB1 (P-glycoprotein) maybe associated toxicity and efficacy.

Pre-Treatment Risk Stratification

Over the past twenty years there has been continued debate regarding the risk stratification of patients with ALL with different groups using the above clinical, immunophenotype, cytogenetics and molecular tests to variably group patients into those that are standard risk, high risk or very high risk of having a leukemia relapse. As discussed, many of these discrepancies may be related to the type of treatment regimens used (adult vs pediatric-based), and whether MRD analysis is taken into consideration in risk stratification.

Recent studies have found that, using pediatric-based protocols, most cytogenetic abnormalities are not independent predictors except for certain abnormalities, such as KMT2A-based abnormalities, t(9;22) and possibly hypodiploidy.^{21, 45} Given the poor prognosis of patients with Ph+ve ALL, the initial risk stratification for all patients should be based on the presence or absence of t(9;22)/BCR-ABL1. Amongst Ph-ve patients the NCCN considers those with hypodiploidy (<44 chromosomes), t(v;11q23)/KMT2A rearrangements or complex karyotype (≥5 chromosomal abnormalities) as high risk.⁸

Although prior studies have shown that a WBC > 30 for B-cell ALL and >100 for T-cell ALL were important risk factors,²⁰ MRD has since been demonstrated to be a more important predictor on multivariate analysis (discussed below). However, age remains an important predictor of outcome in nearly all studies, with patients > age 30-35 having worse outcomes than so-called AYA (adolescent and young adult) patients.²⁰

Recent evidence suggests that molecular profiling, and specifically the detection of a Ph-like genetic signature as discussed, may be the most important pre-treatment predictor of outcome in adults and children with BCR-ABL negative B-ALL. However, detection is time consuming and labour intensive, and is not routinely available at most centres, including in Alberta.

Table 3: Pre-treatment risk stratification factors in ALL patients treated with ‘adult’ chemotherapy regimens.¹

Study Group	Age	WBC	Immunophenotype	Cytogenetics	Others	Definition of Risk Group
CALGB ⁸²	>60	>30		Ph+, t(4;11)	L3, Med -	SR = 0-1 HR = 2-4
GIMEMA ⁸³	>30	>50		Ph+	Prephase	
JALSG ⁸⁴	>30	>30		Ph+		SR = 0 IR = 1 HR = 2/Ph+
MDACC ¹²	-	>50		Ph+	ECOG 3-4, L2, d14 BM+	SR = 0-1 IR = 2-3 HR >3
GOELAMS ⁸⁵	>35	>30	B-Cell	Ph+, t(4;11), (t1;19)	CR > 1c	SR = 0 HR1 = 1-2 HR2 = 2-3
LALA ⁸⁶	-	>30	Myeloid Markers Cd10 and CD20 negativity	Ph+, t(4;11), 11q23, (t1;19)	CR > 1c, CNS +	SR = 0 HR ≥ 1, Ph+, CNS+
PETHEMA ⁸⁷	30-50	>25		Ph+, t(4;11), 11q23, (t1;19)		SR = 0 HR ≥ 1
MRC-ECOG ¹⁹	>35	>30 (B-Cell) >100 (T-Cell)		Ph+		SR = 0 HR ≥ 1
HOVON ⁸⁸	-	>30 (B-Cell) >100 (T-Cell)		Ph+, t(4;11), t(1;19)	CR > 4 weeks	SR = 0 HR ≥ 1
GMALL ⁸⁹	15 - 55	>30 (B-Cell)	Pro-B Early/Mature T	Ph+, t(4;11)	CR > 3 weeks	SR = 0 MRD-HR ≥1, MRD + VHR = Ph+
NILG ⁴⁶	-	>30 (B-Cell) >100 (T-Cell)	Pro-B Early/Mature T	Ph+, t(4;11), adverse cytogenetics	CR > 1c	SR = MRD – HR = MRD +

Study Group	Age	WBC	Immunophenotype	Cytogenetics	Others	Definition of Risk Group
						VHR = Ph+, t(4;11)+

SR – Standard Risk; HR – High Risk; IR – Intermediate Risk; VHR – Very High Risk; CR – Complete Remission; ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia; 1c – 1 cycle of chemotherapy; BM – Bone Marrow; MRD – Minimal Residual Disease

Table 4: Pre-treatment risk stratification factors in ALL patients treated with ‘paediatric’ chemotherapy regimens.

Study Group	Age	WBC	Immunophenotype	Cytogenetics	Others	Definition of Risk Group
FRALLE 93 ⁹⁰	>15	>50		t(9;22), t(4;11); Hypodiploidy, Tetraploidy, slow response to prednisone/chemotherapy		SR = 0 HR ≥ 1
DCOG ⁹¹				t(9;22), MLL rearrangements, slow response to induction		Not specified
DFCI - 91 - 01 ⁹²	<2 or >9	>20	T-cell	Ph+, Mediastinal mass, CNS leukemia,		SR = 0 HR ≥ 1
DFCI - 95 - 01 ⁹²	<1 or >10	>50	T-cell	Ph+, Mediastinal mass, CNS leukemia,		SR = 0 HR ≥ 1
PETHEMA ⁹³		>30	-	t(9;22), t(1;19), t(4;11), MLL rearrangements.		SR = 0 HR ≥ 1
GRAALL ⁹⁴		>30 – B-cell		CNS involvement t(4;11) or <i>MLL-AF4</i> fusion transcript, t(1;19) and/or <i>E2A-PBX1</i> fusion transcript, low hypodiploidy (30 to 39 chromosomes or DNA index 0.85), near-triploidy (60 to 78 chromosomes or DNA index of 1.30 to 1.69). CsR and/or ChR, absence of CR after the first induction course, Ph+		SR = 0 HR ≥ 1

Study Group	Age	WBC	Immunophenotype	Cytogenetics	Others	Definition of Risk Group
DFCI ²⁰	≥35	>30 B-Cell >100 T-Cell		MLL		Not specified
DFCI ⁴⁵	≥34	>30 B-Cell >100 T-Cell				Not specified
DFCI ⁹⁵	≥35	≥35 B-Cell ≥100 T-Cell		MLL, Ph+,		Not specified

SR – Standard Risk; HR – High Risk; IR – Intermediate Risk; VHR – Very High Risk; CR – Complete Remission; ECOG – Eastern Cooperative Oncology Group; Ph – Philadelphia; 1c – 1 cycle of chemotherapy; BM – Bone Marrow

Recommendations:

All patients should be classified as having B-cell or T-cell ALL based upon immunophenotyping results. Although some of the above noted prognostic factors are beyond the scope of routine clinical laboratories, all patients, should undergo cytogenetic evaluation and, if unsuccessful, FISH for the determination of the most clinically significant abnormalities, in particular *BCR-ABL* and *KMT2A* gene rearrangements. There is no convincing evidence that other cytogenetic abnormalities or cell surface markers add to risk-stratification when using paediatric or paediatric inspired protocols, except possible for low hypodiploidy.

MRD Assessments in the Management of Patients with ALL:

Measurable (or minimal) residual disease (MRD) refers to the detection of small amounts of residual disease, undetectable by morphology. Techniques for MRD detection include multiparameter flow cytometry (MPFC) or molecular techniques. For BCR-ABL+ ALL, molecular detection is readily performed by qRT-PCR for BCR-ABL1, and is regarded as the gold standard for MRD detection. For BCR-ABL negative ALL, many European studies have used immunoglobulin gene rearrangements (IgR) for MRD detection; however, this technique is labour intensive and requires detection of the specific rearrangement for each patient. Molecular IgR testing can also be performed by next generation sequencing (NGS), commonly known as ClonoSEQ[®]. The latter technique has a sensitivity as low as 10⁻⁶, is FDA approved, and is now widely used in the U.S. This test is not yet available in Canada; samples need to be sent to the U.S. and testing is limited by high cost. Consequently, MPFC is widely used for MRD detection due to its ease, and has a sensitivity of 10⁻⁴; it is the technique currently used in Alberta.

Based on the paediatric literature, a number of studies over the past 15 years have explored the role of MRD in adults with ALL. Most of these have suggested that MRD may be the single most important factor predicting clinical outcomes.⁹ A number of investigators have described differences in patterns and

dynamics of clearance of MRD between adult and childhood ALL as well as between B- and T- cell ALL. Foroni et al. noted that MRD decreased faster in children than in adults particularly in the first 6 months of CR⁹⁶ while Parekh et al. noted that MRD clearance was slower with T-ALL.⁹⁷ Bruggemann and colleagues measured MRD at 9 different time points ranging from 11 days post-induction up to 52 weeks post induction.⁹⁸ Only a minority of patients had undetectable MRD at day +11 while at 6 weeks approximately 50% had undetectable MRD.

Several groups have explored the prognostic value of MRD in adult ALL patients. Bruggman and colleagues noted that a combination of MRD measurements at day 11, day 24 and 16 weeks could classify patients into those with a low likelihood of ALL relapse (MRD –ve at day 11 and day 24), high likelihood of relapse (MRD + at week 16) or intermediate risk of relapse (all others).⁹⁸ Similar findings were noted by Bassan and colleagues who measured MRD at week 10 and week 22 post induction chemotherapy.⁴⁶ Regardless of whether they were SR, HR or VHR by traditional criteria, patients who were MRD negative had significantly better DFS relative to those that were MRD positive.

Whether treatment intensification can negate the negative effects of MRD has also been investigated by several investigators. Bassan and colleagues assessed MRD at week, week 16 and week 22.⁴⁶ Patients that were MRD negative or with unknown MRD status but standard risk by traditional criteria received maintenance treatment only while patients that were MRD positive or with unknown MRD but high risk or very high risk by traditional criteria received an allogeneic SCT or autologous blood stem cell harvest/reinfusion with subsequent maintenance therapy. MRD positive patients receiving either SCT or intensive chemotherapy had improvements in DFS with no significant difference between those that received SCT and intensive chemotherapy. Moreover, patients who became MRD negative had improved DFS relative to those who remained MRD positive. Similar results were noted by Gokbuget et al. where 5 year CCR improved for MRD positive patients undergoing an allo SCT.⁹⁹ Ribera and colleagues noted that allo SCT in MRD –ve patients was unnecessary and counterproductive as it led to worse DFS and overall survival both in the whole series and an intention to-treat-analysis.¹⁰⁰

Beldjord et al. assessed 423 adult patients with Ph-negative ALL treated with a pediatric protocol.²¹ MRD1 was evaluated at 6 weeks after induction initiation and MRD2 after the first consolidation phase i.e. 12 weeks after induction initiation. As expected, MRD2 and MRD1 levels strongly correlated in this cohort. Overall, 265 patients achieved a MRD response at MRD1, 57 achieved it at MRD2 only, and 49 did not achieve it at either time-point. At 5 years, CIR was estimated at 24.7% in patients who reached a MRD level lower than 10^{-4} at MRD1, while it was 56.0% in those who reached this level at MRD2 only or never reached it, respectively. The value of traditional risk factors was examined in this population of patients treated with a pediatric-inspired protocol in multivariable analysis, against MRD1 response. Based on multivariate analysis, MLL gene rearrangement, IKZF1 gene deletion, and MRD1 level $\geq 10^{-4}$ were significant factors in B-ALL patients whereas a high-risk genetic profile and MRD1 level $\geq 10^{-4}$ were significant in T-ALL patients. Based on these results, high-

risk patients could be defined as patients with MRD1 level $\geq 10^{-4}$; and/or unfavorable genetics, defined as t(4;11) translocation or other MLL gene rearrangement and/or IKZF1 gene deletion in B-ALL; and 2) no NOTCH1/FBXW7 mutation and/or N/K-RAS mutation and/or PTEN alteration in T-ALL patients. MRD level seemed to be the predominant predictor in B-ALL patients with the risk further refined by genetic features. In contrast, in T-ALL patients both the oncogenetic classification and MRD response were the major predictors of relapse. In both lineages, patients with high-risk genetic characteristics and poor MRD1 response experienced a worse outcome.

A study by the GRAALL group, using a pediatric inspired protocol for adults with B-ALL, evaluated the role of allogeneic HSCT according to MRD response with induction therapy.⁴⁷ Patient who were MRD positive, defined as a level $> 10^{-3}$ following induction therapy, had a significantly higher relapse rate and inferior OS as compared to those who achieved a level $< 10^{-3}$. Furthermore, those with MRD levels $> 10^{-3}$ who underwent subsequent HSCT in CR1 had a significantly superior RFS and OS as compared to those who were not transplanted. In contrast, those with MRD levels $< 10^{-3}$ following induction did not benefit from HSCT. These effects were seen for both B-ALL and T-ALL.

The Edmonton group subsequently analyzed outcomes following DFCI induction therapy.¹⁶⁵ Between 2014-2024, 89 patients with BCR-ABL negative ALL underwent induction therapy with this protocol; MRD post-induction was assessed by multiparameter flow cytometry, with a sensitivity of 0.01%. Of 71 patients who achieved CR and had initial bone marrow involvement, 55% were MRD negative and 38% were MRD positive at $\geq 0.1\%$ of mononuclear cells. The disease-free survival (DFS) was 80% in those achieving MRD negativity post-induction vs. 46% in those with MRD levels $\geq 0.1\%$ ($p=0.022$). These results essentially mirror those reported by the GRAALL group as described above. However, these results do not take into consideration the potential role of multiple cycle of blinatumomab in post-remission therapy; this will be discussed later.

A German study found a strong association between MRD positivity and a Ph-like genotype; Ph like B-ALL patients only achieved a 33% MRD negativity rate, as compared with 79% for Ph negative and non-Ph-like B-ALL patients ($p=0.02$).¹⁷⁵ Therefore, MRD may represent a surrogate marker for a more resistant disease biology which is more destined to relapse with conventional chemotherapy.

Although both flow and molecular-based MRD testing are considered valid for assessing MRD in B-ALL, a study from MD Anderson Cancer Center compared both techniques in B-ALL patient post-induction chemotherapy. Patient who were MRD negative by ClonoSEQ post-induction had no relapses, while those who were MRD negative by flow but positive by ClonoSEQ had a 29% cumulative incidence of relapse using their regimen.¹⁷⁹ This suggests that ClonoSEQ is superior at detecting very low levels of MRD and in predicting relapse.

Treatment of MRD positive B-ALL:

Blinatumomab is a bispecific tumour-engaging (BiTE) antibody with an anti-CD19 domain that binds to B-cells, including B-ALL cells, and an anti-CD3 domain that engages T lymphocytes to lyse the B cells. A large European study¹⁰¹ was recently published, evaluating the role of blinatumomab in 116 B-ALL patients in hematologic CR with MRD positivity, defined as a level > 0.1% by qRT-PCR. Patients were permitted to receive up to 4 treatment cycles, and could undergo allogeneic HSCT at any time after the first cycle. Overall, 78% of patients achieved an MRD negative state, with a sensitivity of 10^{-4} , after one blinatumomab treatment cycle. Two additional patients achieved this after 2 cycles. Of patients in first CR, 83% achieved MRD negativity. The treatment was well-tolerated. The median OS of the patients who achieved MRD negativity was 38.9 months, vs. 12.5 months in those who did not achieve MRD negativity ($p=0.002$); corresponding RFS were 23.6 vs. 5.7 months, respectively ($p=0.002$). With a median follow-up of 24 months, 49% of patients who underwent subsequent HSCT remained in continuous CR, as compared with 25% who did not undergo HSCT. By comparison, in Edmonton BCR-ABL negative B-ALL patients who were MRD positive at a level > 0.1% by flow cytometry after DFCI induction therapy were treated with intensified chemotherapy, using cycles 1A and 1B of Hyper-CVAD, between 2013-2018. Of 13 patients, only 5 (38%) were able to achieve MRD negativity; treatment was associated with considerable toxicity, including severe myelosuppression and mucositis.

These data indicate that (1) blinatumomab is able to induce a high rate of MRD negativity, usually after one cycle, with good tolerance, (2) patients who achieve MRD negativity have superior outcomes compared with those who do not, and (3) intensified chemotherapy is less effective at inducing MRD negativity and is associated with considerably more toxicity.

For *BCR-ABL* positive ALL the situation is more complex, as there are different MRD assays available. These include *BCR-ABL* PCR, which detects any cells harboring this mutation, and flow or molecular immunoglobulin gene rearrangement (IgR) assays, both of which detect the lymphoblast population. Studies have shown that approx. 25% of patients who become MRD negative by flow or IgR will remain *BCR-ABL* positive by PCR.^{167,168} Cell sorting studies have determined that in these cases the *BCR-ABL* abnormality appears to reside in the myeloid population¹⁶⁷; this entity has been called CML-like ALL by some groups. Please see the section on Treatment of *BCR-ABL* Positive ALL for a detailed discussion of prognosis and treatment approaches based on results of these MRD assays.

Recommendations:

These data indicate that MRD assessment provides critical prognostic information in adults with ALL. There is convincing evidence in pediatric and adult ALL that a high level of MRD at the end of induction therapy is associated with a higher relapse rate. Furthermore, the persistence of MRD post-blinatumomab consolidation therapy, or its later re-emergence, predict for a high risk of relapse. In contrast, negative MRD results are associated with a favorable prognosis. It is therefore

recommended that all patients have MRD ascertained at the end of intensive induction therapy. If positive, MRD should be reassessed after one cycle of post-remission blinatumomab, and periodically thereafter. For T-ALL patients who are MRD positive after induction chemotherapy, intensified chemotherapy or nelarabine would be appropriate.

C. Treatment of BCR-ABL negative ALL

In general, the treatment of ALL is complex consisting of several different chemotherapy cycles and, for some patients, stem-cell transplantation.¹ A number of different approaches have been used as discussed below.

Adult-based regimens:

Starting in the 1960s, researchers at St. Jude Children's Research Hospital designed combination therapies of available anti-leukemia drugs that were delivered in a sequence of extended courses of therapy.⁹ Since then several multidrug combinations have been developed centered on a vincristine, prednisone, and anthracycline combination, with or without asparaginase and cyclophosphamide. This concept was modified in children to the Berlin-Frankfurt Munster (BFM) ALL model and later, by Hoelzer et al., to adult ALL.^{11, 102} Despite variations in chemotherapy regimens, variable use of allogeneic SCT or auto SCT the 5 year overall survivals ranged from 35 – 60% in various subgroups with induction mortality ranging of 5-10%.

The second treatment model pioneered at the M.D. Anderson Cancer Center consists of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate and cytarabine (Hyper-CVAD). The regimen consists of a total of eight courses: four courses of hyper-CVAD (courses 1, 3, 5, and 7) alternate with four courses of MTX and HIDAC (courses 2, 4, 6, and 8).^{103, 104} In the original report the mortality was 6% and the overall CR rate was 91%. The estimated median survival time was 35 months with a 5-year estimated survival of 39%. Younger age was associated with better survival (age <30 had estimated 5-year survival rate of 54% vs. age > 60 estimated 5-year survival rate of 25%). The addition of rituximab was associated with CCR and OS rates of 60% and 58%, respectively. Treatment with Rituximab-Hyper-CVAD was associated with improvement in 3-year CRD rates compared with hyper-CVAD (78% vs. 53%). In patients age < 60 improvements in 3-year OS (75% vs. 47%; $P=0.003$) rates favoring rituximab were observed.¹⁰⁵

Pediatric-based regimens:

A third approach was the adoption of pediatric protocols or “pediatric inspired” regimens, particularly for adolescents and young adults variably defined as patients 15 to 35-45 years old.^{1, 106} These regimens have common features, including significantly increasing the non-myelosuppressive agents such as vincristine and steroids, using much higher cumulative doses of asparaginase for prolonged

asparagine depletion, and administering very early and extended intrathecal methotrexate together with high-dose systemic methotrexate. Several studies from Europe and the USA reported that pediatric inspired approaches are feasible in adolescents and adults, and have produced superior results (Table 5 and 6). These studies have shown that prolonged administration of non-myelosuppressive agents such as asparaginase, vinca alkaloids and steroids is feasible and tolerated in a substantial portion of adults. Based on these studies, pediatric based regimens have now been widely accepted as the standard of care for younger adults with ALL.

Table 5: Outcomes of adolescents and young adults treated on pediatric protocols.

Study	Number	Age Range	Outcomes		
			Complete Remission	Mortality	Overall Survival
LALA 94 vs. FRALLE- 93 ⁹⁰	FRALLE - 77 LALA - 107	15 - 20	FRALLE - 94% LALA - 83%		FRALLE - 5 year OS - 78% ± 11%; 5 year DFS - 72%, 5 year EFS - 67%; 5-year RFS --> 77% LALA - 5 year OS - 45%; 5 year DFS- 49%; 5 year EFS - 41%; 5-year RFS --> 49%
DCOG vs. HOVON ⁹¹	DCOG – 47	DCOG - 15 - 18	DCOG - 98%	DCOG - 15 - 18 - 4% (5 years TRM)	DCOG - 15 - 18 - 5 year OS - 79 % - 5; 5 year DFS - 71 %; 5 year EFS - 69%; 5 year CIR - 27%
	HOVON - 44	HOVON - 15 -20	HOVON 15-18 - 91%	HOVON - 15-18 - 25% - (5 year TRM)	HOVON - 15-18 - 5 year OS - 38% ; 5 year DFS - 37 %; 5 year EFS - 34%; 5 year CIR - 55%
			HOVON 19- 20 - 90%	HOVON - 19 - 20 21% (5 year TRM)	HOVON - 19 - 20 - 5 year OS - 45% ; 5 year DFS - 38 %; 5 year EFS - 34%; 5 year CIR - 50%
UKALL vs ALL97 ¹⁰⁷	UKALL - 67	15-17	ALL97 - 98%		ALL97 - 5 year - 71%; 5 year - EFS - 69%
	ALL97 - 61		UKALL - 94%		UKALL - 5 year - 56%; 5 year EFS - 49%
DFCI ⁹²	DFCI - 51	15 - 18	94%		5 year OS - 81%; 5 year DFS - 78%
PETHEMA ⁹³	Age 15 - 18 = 35	15 - 30	Age 15 - 18 --> 94%	Age 15 - 18 --> 1 out of 35 patients	Age 15 - 18 --> 6 years - 77%; 6 year EFS - 60%

Study	Number	Age Range	Outcomes		
			Complete Remission	Mortality	Overall Survival
	Age 18 - 30 = 46		Age 18 - 30 --> 100%	Age 18 - 30 --> 0/46 patients	Age 18 - 30 --> 6 years - 63%; 6 years - 63%
CCG vs. CALGB ²⁵	CCG - 197	16 - 20	CCG - 90%		CCG - 7 year - 67%; 7 year EFS - 63%
	CALGB - 124	16 - 20	CALGB - 90%		CALGB - 7 year - 46%; 7 year EFS - 34%
CCG 1961 ⁴⁰	262	16 - 21			5-year overall survival - 77.5%; 5-year EFS - 71.5%
St. Jude XV ¹⁰⁸	45 on XV study	15 - 18			5-year overall survival - 87.9%; 5 years EFS - 86.4%

Table 6: Outcomes of adult patients using paediatric protocols.

Study	Number	Age		Complete Remission	Outcomes	
		Range	Median		Mortality	Overall Survival
GRAALL vs. LALA - 94 ⁹⁴	GRAALL - 225	15 - 55	31	GRAALL - 93.5%	GRAALL - 6%	GRAALL: OS 3.5 years --> 61%; EFS - 57%; CIR - 31%
	LALA - 712	15 - 55	29	LALA - 88%	LALA - 4.5%	LALA: OS 3.5 years --> 41%; EFS - 33%; CIR - 55%
						GRAALL Age 15 - 45: OS 3.5 years - 64%; EFS - 58%
						GRAALL Age 46 - 60: OS 3.5 years - 47%; EFS - 46%
DFCI ²⁰	DFCI - 85	18 - 60	37	< 35 = 98%	0% age < 35	3 year OS - 67%
				> 35 yo - 81%	8% age - 36-49	5 Year OS - 63%
				Combined - 89%	73% age >50	DFCI Age 18 - 35: 3 year OS - 83%; RFS - 77%
						DFCI Age 35 - 60: 3 year OS - 52%; RFS - 60%

Study	Number	Age		Outcomes		
		Range	Median	Complete Remission	Mortality	Overall Survival
DFCI ⁴⁵	Age 17 - 60 --> 156 17 - 34 --> 73 34 - 50 --> 54 50 - 60 --> 29	17 - 60	37	17 - 34 = 99% 34 - 50 = 87% 50 - 60 = 90% Combined - 93%		DFCI Age 18 - 35: 5 year OS - 80% DFCI Age 35 - 60: 5 year OS - 50% Age 17 - 34 5 year OS = 80% Age 34 - 50 5 year OS = 50% Age 50 - 60 5 year OS = 62% Combined 5 year OS - 66%; 5 Year DFS - 70% age < 34 and low WBC (n = 57): 85% (71–93%) age < 34 and high WBC (n = 15): 57% (28–78%) age > 34 and low WBC (n = 73): 57% (44–68%) age > 34 and high WBC (n = 10): 30% (7–58%)
DFCI ¹⁰⁹	51	60 - 79 (12>70)	65	BCR - ABL Positive -> 81% BCR - ABL Negative --> 71% Combined - 75%	20%	BCR - ABL Positive --> 47.3 % at 5 years BCR - ABL Negative --> 40.5% at 5 years
DFCI ⁹⁵	92	18-50 18-29 30-50	28 48 44	85% 16/18 = 89% T-cell 62/74 = 84 % B-cell	1/92 patients	4 Year OS 67%; DFS - 69%; EFS - 58% Age 18 - 29: 4 Year OS - 68%; DFS - 70%; EFS - 55% Age 30 - 50: 4 Year OS - 65%; DFS - 67%; EFS - 61% T-cell ALL: 4 year OS - 76%; DFS - 87%; EFS - 77%

Study	Number	Age		Outcomes		
		Range	Median	Complete Remission	Mortality	Overall Survival
				14/18 = 78% Ph - +ve 64/74 = 86% Ph - -ve		Ph -ve/B-cell: 4 Year OS - 68%; DFS - 66%; EFS - 57% Ph +ve/B-cell: 4 year OS - 53%; DFS - 54%; EFS - 42% WBC < 20: 4 year OS - 80 WBC > 20: 4 year OS - 45%
DFCI ¹¹⁰	30	51-72	58	age > 50 = 67%	Age > 50 = 10%	62% at 1 year; < 20% at 3 years (based on survival curve)
CALGB ¹¹¹		17-39	24		3%	EFS 59% at 3 years OS 73% at 3 years

Adolescents and Young Adults (AYA):

Adolescents and young adults have been variably defined as those aged 15 – 35/40 years old. A multitude of accumulating evidence suggests that this group of patients is best treated with a pediatric or a pediatric inspired protocol. Ram et al. conducted a systematic review of 11 studies that compared adult and pediatric protocols.¹¹⁵ Overall, all-cause mortality, relapse rates and non-relapse mortality were lower in the pediatric groups whereas CR rates and EFS were higher in the pediatric groups. It is important to note that in many of these studies the median age ranged from 12.9 – 31 with only two studies including patients over age 55.

Boissel and colleagues compared the outcomes of adolescents aged 15 – 20 years of age treated with the adult LALA -94 vs. the pediatric FRALLE-93 protocol⁹⁰. The LALA-94 trial included 100 patients (median age 17.9 years) and the FRALLE-93 trial included 77 patients (median 15.9 years) 15- 20 years of age. The CR rate was significantly higher in the FRALLE-93 trial (94 %) than the LALA-94 trial (83 %). The 5 year-EFS was also worse in the LALA-94 trial (67 %) compared to 41 % in the FRALLE-93 trial. In the Dutch study by de Bont and colleagues⁹¹, adolescents aged 10 – 20 years old were treated with the Dutch Childhood Oncology Group (DCOG) or adult Dutch-Belgian Hemato-Oncology Cooperative Study Group (HOVON) adult protocol. For 15–18-year-old adolescents, the 5- year event-free survival (EFS) when treated on pediatric protocols was 69%, which is significantly higher than when treated on adult protocols (34%).

Stock and colleagues²⁵ assessed the outcomes of 321 adolescents and young adults ages 16 – 20 years treated on either the paediatric Children's Cancer Group (CCG) protocols (N= 197, median age 16) or the CALGB group protocols (N= 124, median age 19). EFS at 7 years for the 25 CALGB

patients aged 16 to 17 years was 55% which was not different than the CCG patients ($P = .49$). Notably, 18-20 year olds treated with the CALGB protocol fared significantly worse compared to 18-20 year olds treated with the CCG protocol (7 year EFS 29% vs. 57%). More frequent and earlier CNS prophylaxis was incorporated into the CCG trials leading to a lower CNS relapse rate of 1.4% in the CCG arm and 11 % in the CALGB arm.

The GRAALL study group evaluated the outcomes of 225 adult patients aged 15 to 60 treated with the GRAALL-2003 protocol and compared the outcomes with 712 patients aged 15 – 55 treated on the adult LALA-94 protocol. The overall CR rate for the 225 GRAALL-2003 treated patients was 93.5% with 6% induction mortality. A significantly longer OS was observed in patients aged 15 - 45 at 42 months when treated with the GRAALL-2003 protocol. Storrington et al also assessed the outcomes of adults treated with the modified DFCI pediatric regimen at the Princess Margaret Cancer Centre.²⁰ Between 2000 and 2006 85 adults aged 18 -60 with BCR-ABL negative ALL were treated. CR was achieved in 89% of cases. Of these, only age predicted for achievement of CR. For patients aged ≤ 35 years, the complete response rate was 98% (41/42). For patients age < 35 the median 3 year RFS was 77% and the median 3 year OS was 83%.

The native *E. coli* asparaginase used in the DFCI 91-01 protocols is no longer available in Canada, and has been replaced by pegylated asparaginase (Pegaspargase). This should be given no more frequently than once every 3 weeks in adults due to its long half-life (see Appendix A-C for protocol). Although pegaspargase was initially given at a dose of 2000 U/m², many centres have experienced excessive rates of hepatotoxicity and pancreatitis in adults at this dose. Toxicity has been found to be higher in patients with BMI > 30 and/or steatohepatitis. Consequently, the dose has been reduced to 1000 U/m² in most centres, including in Alberta (see Appendix A-C for new dosing). As will be described later, dosing may need to be modified further based on asparaginase levels and toxicity.

Patients Aged 35 - 55/60:

The use of pediatric protocols for the treatment of adolescents has inspired some groups to explore the use of pediatric protocols in older adults however the data are not clear whether this represents a significant difference relative to adult protocols. When using the paediatric GRAALL-2003 protocol improvements in EFS and OS were noted at 42 months but only for patients $< \text{age } 45$.⁹⁴ Similarly, Storrington and colleagues, when using a modified DFCI paediatric regimen²⁰ for adults aged 18 -60 noted that the complete response rate decreased with increasing age – from 86% for patients aged 36–49 years, to 73% for patients aged ≥ 50 years. In addition, there was a trend for an increase in induction mortality by age: 0% for age ≤ 35 years, 8% for age 36–49 years, and 20% for age ≥ 50 years. In addition, age > 35 was significantly associated with inferior 3 year - OS (83% vs. 52%). In an updated analysis,

Brandwein et al. assessed the outcomes of 156 adults with BCR-ABL negative ALL treated with a modified DFCI. Again, the CR rate decreased with increasing age. The CR rate amongst those age

<34 was 99% while for those age 34-50 the CR rate was 87% and those aged 50-60 was 90%. The 5 year OS amongst patients aged <34 was 80% while those for patients aged 34-50 was 50% and those aged 50-60 was 62%. Whether the decreased rate of survival seen in patients aged 34-50 was due to an increased use of allo- SCT in this age group is unknown. DeAngelo and colleagues recently presented the results of their studies on the use of the DFCI protocol for patients 18-50 years old. They found no statistically significant difference in the outcomes for patients that were 18-29 years old or those that were 30-50 years old in terms of 4 years DFS (70 vs. 67%), 4 year EFS (55 vs. 61%) or 4 year OS (68 vs. 65%).

Patients Aged >55-60:

Fit patients: The outcome of patients above age 60 treated with standard ALL chemotherapy has been generally poor. Larson et al. using the CALGB 8811 protocol noted a 3 year OS of only 17% with a median survival of only 1 month.⁸² Brandwein et al. noted similar results when using a multitude of different adult based chemotherapy regimens.¹¹⁶ In their study the 3 year OS was only 18.4%. Using the HyperCVAD protocol Kantarjian et al. noted a 5 year OS of 17%.¹² Thus, it appears that the majority of older patients with ALL will succumb to their disease although some older patients may remain long-term survivors.

The optimal treatment in these patients is unclear. The Princess Margaret group evaluated the use of a modified protocol in this older subset of patients (Appendix B).¹⁰⁹ Modifications from the full-dose DFCI 91-01 protocol during induction included the substitution of two dexamethasone pulses instead of daily prednisone, reduction of the methotrexate dose from 4 g/m² to 40 mg/m², reduction in the asparaginase dose and removal of one vincristine dose. In the intensification phase seven cycles were given instead of 10, the dexamethasone dose was reduced to 6 mg PO BID and the asparaginase was reduced. In the maintenance phase the dexamethasone dose was again reduced to 6 mg PO BID. Median age was 65 (60 – 79), 12 patients were over the age of 70, 35 patients were BCR-ABL negative and 16 were BCR – ABL positive. The CR rate was 75% for the entire cohort with 20% induction mortality. The estimated 5-year OS was 40% for the BCR-ABL1 negative patients, and 47% for the BCR-ABL1+ patients. The estimated 5-year OS for BCR-ABL1 negative patients presenting with low WBC (defined as <30 x 10⁹/L for B-ALL or <100 x 10⁹/L for T-ALL) was 44%.

Because of the high induction mortality seen in older patients with this regimen (20% at PMH, 25% in Edmonton¹⁶⁵), mainly due to sepsis, there are now attempts to reduce the intensity by reducing or removing mucositis-producing drugs, and a modified reduced intensity induction is now being piloted by the Edmonton group (see Appendix B). This is particularly relevant for B-ALL, with the availability of antibody-based salvage therapies (see below). Clinical trials are also investigating the addition of blinatumomab and/or inotuzumab to reduced intensity chemotherapy upfront in these patients (e.g. Golden Gate Study, NCT04994717). The German GMALL group reported the use of Inotuzumab monotherapy as induction, followed by post-induction chemotherapy, for patients age 55 and older

with BCR-ABL negative B-ALL, with no induction mortality and all 43 patients achieving CR¹⁶⁰. However, these treatment approaches are not currently approved by Health Canada.

Addition of blinatumomab in B-ALL:

A large randomized E1910 trial was recently completed in patients age 30-70 years, evaluating the addition of 4 cycles of blinatumomab as post-remission therapy to a chemotherapy backbone based on a modified MRC UKALL XII/ECOG E2993 protocol¹⁵⁸. Patients who were MRD negative post-induction and received blinatumomab had a 3-year OS of 85% vs. 68% for the chemotherapy only arm (P=0.0002). Results of this study have led to Health Canada approval for the incorporation of 4 cycles of blinatumomab into post-remission chemotherapy for all adult patients with BCR-ABL negative B-ALL, regardless of MRD status. In this trial, MRD positive patients were initially randomized as well, but the protocol was later amended to administer blinatumomab to all MRD positive patients, as this use became widely accepted based on the BLAST study¹⁰¹, as discussed earlier under MRD. A modified DFCI protocol, incorporating 4 cycles of binatumomab, has been created by the Canadian Leukemia Study Group (CLSG), and has been implemented at many Canadian centres, including Alberta (see Appendix C).

In a subgroup analysis of the E1910 trial, patients with KMT2A rearrangements and those with Ph-like genotypes had an excellent prognosis in the blinatumomab arm if MRD negative post-induction. However, patients with low hypodiploid cytogenetics had inferior outcomes and did not appear to benefit from blinatumomab.¹⁵⁸ As described earlier, the latter group is frequently TP53-mutated.

Recommendations for fit adults with BCR-ABL negative ALL:

Patients under age 55-60 who are fit for intensive chemotherapy should receive induction and post-remission therapy using a pediatric-based protocol. In Alberta the standard regimen is the PMH modified DFCI protocol, substituting pegaspargase for native E coli asparaginase, as outlined in Appendix A. For B-ALL patients who achieve a complete remission, 4 cycles of blinatumomab should be incorporated into post-remission therapy, preferably as described in Appendix C, regardless of MRD status. Patients with T-lymphoblastic leukemia/lymphoma should receive the full DFCI regimen without blinatumomab.

For fit patients age >55-60, a modified reduced intensity regimen is recommended in order to reduce toxicity; the modified PMH DFCI protocol for older patients is one regimen being used in Alberta (Appendix B). Given the higher induction mortality in these patients, a reduced intensity induction approach is recommended for B-ALL patients, as outlined in Appendix B). Once a complete remission is achieved, 4 cycles of blinatumomab should be used for B-ALL patients, as described above for the younger patients and in Appendix B.

Unfit patients:

Many elderly patients are unfit for such intensive chemotherapy approaches, due to co-morbidities and overall frailty. For those patients, palliative low-dose chemotherapy may be used. The Spanish

PETHEMA group recently reported outcomes in such patients using weekly vincristine plus dexamethasone with IT chemo, followed by maintenance with 6MP and methotrexate¹⁵⁷. The regimen was well-tolerated; a 54% CR rate was obtained with 10% early deaths; the median OS was 7.6 months and one year OS approx. 20%¹⁵⁷. In some patients with better ECOG PS a single dose of pegaspargase 500 U/m² may be added to induction, but increases the risk of liver toxicity. If a CR is achieved and PS remains good, a slightly more intensified maintenance chemotherapy using the POMP regimen (vincristine, prednisone, 6-MP and weekly oral methotrexate) may be used in an attempt to prolong remission duration. If neurotoxicity becomes an issue, the vinblastine may be used, or the vinca can be deleted.

Patients over age 75, or those age 60-75 with major co-morbidities precluding intensive chemotherapy, should be considered for palliative chemotherapy with corticosteroids and vincristine followed by maintenance therapy. The PETHEMA (aka Ribera) protocol is currently being used in Alberta. Such patients should continue to receive central nervous system prophylaxis and may benefit from incorporation of a CNS phase. Patients who receive a DFCl-type induction and then become unfit for post-remission intensification treatment, may be moved directly to the DFCl maintenance phase.

Role of Allogeneic Stem Cell Transplantation (HSCT) for Ph-/BCR-ABL- ALL:

In the largest adult ALL trial to date (MRC-ECOG UKALLXII/E2993) patients in first complete remission < 50 years were assigned to HSCT if they had a compatible sibling donor while others were randomized to consolidation/maintenance therapy for 2.5 years or to autologous transplant and no further therapy. Patients were considered to be high-risk if they had age >35, WBC >30,000/ mL for B-lineage or WBC >100,000/mL for T-ALL, Philadelphia chromosome positivity, t(4;11), t(8;14), complex karyotype, low hypodiploidy or triploidy. All other patients were considered standard risk. In a donor versus no-donor analysis, patients with a sibling donor had improved OS than those with no donor (53% vs. 45%). In the standard risk group, the OS at 5 years was 62% for patients with a donor compared to 52% for patients with no donor (P=.02). In contrast, for high-risk patients OS was 41% for those with a donor vs. 35% for those without a donor (p=0.2) likely due to the high non-relapse mortality. The 10 year relapse rate was substantially lower in patients with a donor (24% for standard risk and 37% for high-risk) versus those without a donor (49% standard risk and 37% high-risk).¹⁹ The Spanish PETHEMA group reported similar findings in their cohort of high-risk patients defined as those with age 30-50 years old, WBC count >25,000/ mL, Ph +ve, t(4;11)/other 11q23 rearrangements, or t(1;19).⁸⁷ In contrast, two French studies both reported that there was an advantage for high-risk patients having a donor.^{86, 135}

A meta-analysis of 7 studies that included 1274 patients also noted improvements in overall survival for patients with donors relative to those in the no-donor groups undergoing allogeneic stem-cell transplantation. When only high-risk patients were analyzed, the survival advantage was greater.¹³⁶ More recently, Gupta et al. conducted a meta-analysis using individual patient data from a total of 20

trials that included a donor no-donor comparison. Overall survival at 5 years was significantly better in the donor arm (49.9% vs 42.7%, $p=.003$). However, because TRM was much higher in those age >35 both in the donor and no-donor arms there was no difference in OS in this age group. Interestingly, unlike in previous studies and using standardized definitions of high/standard risk, there was no evidence that survival differed by risk category. It was therefore concluded that patients age<35 benefit from HSCT regardless of risk group. Furthermore, by reducing TRM, RIC has the potential to extend the benefit of HSCT to those age>35.

However, the above data applied to patients receiving adult-based protocols. Seftel and colleagues compared 422 Ph-ve ALL patients aged 18-50 years with 108 patients receiving DFCI chemotherapy¹⁵⁵. Expectedly, treatment related mortality was higher in those receiving HSCT (37% vs. 6%). At 4 years, the incidence of relapse was similar for those receiving HSCT and chemotherapy (24% vs. 23%), however, both DFS and OS were improved for those receiving chemotherapy alone (40% vs. 71% for DFS and 45% vs. 73% for OS). Dhedin and colleagues further assessed the role of HSCT in Ph-ve ALL adult patients with at least 1 conventional high-risk factor treated with the paediatric inspired GRAALL 2003 and 2005 protocols.⁴⁷ In all, 522 patients age 15 to 55 years old were candidates for HSCT in first complete remission. Among these, 282 (54%) received a transplant in first complete remission while 240 (46%) did not. As with previous studies, the lower CIR observed in the HSCT was counterbalanced by a higher NRM. When analyzing HSCT in CR1 as a time-dependent event RFS and OS were not significantly improved in the HSCT cohort. No significant effect of HSCT on RFS was noted in patients younger or older than age 45 or on any prespecified baseline risk factor. RFS and OS were significantly longer, however, in patients who presented with morphologic poor early BM blast clearance or in late CR patients. Furthermore, HSCT was associated with longer RFS in patients with postinduction minimal residual disease (MRD) $>10^{-3}$ but not in good MRD responders. In contrast, Edmonton data in patient who were MRD positive after DFCI induction therapy did not find any difference in OS between patients who underwent HSCT vs. those who continued on DFCI chemotherapy.¹⁶⁵

Limited data from the E1910 study, adding 4 cycles of Blinatumomab to post-remission therapy, found favourable results in MRD positive patients, with 3 year OS $>70\%$ ¹⁸⁰, most of whom were not transplanted. This questioned the need to routinely transplant patients who are MRD positive post-induction, provided they can rapidly be converted to MRD negativity with blinatumomab. The current approach used by other groups (such as the German GMALL group) consider patients for HSCT only they remain if MRD positive after one cycle of blinatumomab (N. Gokbuget, personal communication). However, the genotype also needs to be taken into consideration: Patients with high-risk features, such as Ph-line genotype, KMT2A rearrangement, low hypodiploidy or TP53 mutation, should be considered for HSCT if MRD positive post-induction chemotherapy. However, these considerations are not based on high level evidence and require confirmation with further studies.

For pediatric-based protocols, asparaginase is a critical agent in achieving the high cure rates reported. There is evidence in both pediatric and adult studies with the DFCI protocol that the inability to deliver the intended asparaginase dosing during intensification (defined as $\geq 80\%$) is associated with a higher relapse rate.^{20, 137} Therefore, the inability to deliver effective asparaginase dosing (e.g. due to pancreatitis) places the patients in a higher risk category and warrants consideration of allogeneic HSCT.

Patients with ETP-ALL are also considered a high-risk group for relapse based on published data.^{77,78} Therefore, most physicians recommend referring these patients for HSCT in CR1. For other T-ALL patients, the prognosis of patient who are MRD negative post-induction remains excellent, based on the DFCI and GRAALL data; however, given the limited ability to salvage relapsed T-ALL patients, MRD positive patients should be considered for HSCT.

Transplant recommendations for Ph-/BCR-ABL- ALL:

Most patients with Ph-/BCR-ABL negative B-ALL treated with a paediatric protocol who attain an MRD negative complete remission with induction therapy plus 1 cycle of blinatumomab are at low risk of subsequent relapse and may continue on chemotherapy + blinatumomab without HSCT. Given that patients with KMT2A rearrangements remain a high-risk group with pediatric based regimens, HSCT should be considered in patients with this abnormality if MRD positive post-induction chemotherapy. However, KMT2A patients who are MRD negative may continue on chemotherapy + blinatumomab without transplant. Patients with low hypodiploidy, esp. if TP53 mutated, should also be considered for HSCT if MRD positive post-induction.

Failure to achieve a complete hematologic remission after the first induction cycle is also generally considered a high-risk feature, and HSCT is also recommended for these patients. Although high presenting WBC has been identified in the past as a high-risk feature, its prognostic value is superseded by MRD based on data from GRAALL. Failure to deliver effective asparaginase dosing during intensification (e.g. due to early onset pancreatitis) should also warrant consideration of SCT.

Patients who are persistently MRD +ve at $>10^{-4}$ (or $>0.01\%$) after induction chemotherapy plus one cycle of blinatumomab are at higher risk of relapse. Such patients should be considered for HSCT, optimally after receiving further cytoreduction to attain an MRD negative state prior to transplant. If not considered suitable for HSCT, CAR-T therapy may be considered. If not proceeding to HSCT or CAR-T, patients should be continued on the DFCI protocol, completing 4 cycles of blinatumomab if B-ALL. Close monitoring of MRD status is recommended in such patients.

Patients with T-ALL should be considered for HSCT if they are MRD positive post-induction chemotherapy, as they remain at high risk for relapse and salvage approaches are limited. Patients with ETP-ALL are at particularly high risk of relapse and should also be considered for HSCT in CR1.

D. Treatment of Philadelphia Chromosome (BCR-ABL) Positive ALL:

Tyrosine kinase inhibitors (TKI's) have become the standard of care for Ph+/BCR-ABL+ ALL and have led to improvements in the outcomes for all age groups.¹ The earliest TKI used in ALL was imatinib. Although, different chemotherapy regimens and schedules of imatinib have been assessed, all showed improvements in overall survival and reduction in the relapse rate.¹¹⁸⁻¹²⁰ In the first large study done by the French GRAAPH-2003 group, the combination of imatinib with induction and post-remission therapy¹²¹ led to higher estimated OS (65% vs. 39%), lower CIR (30% vs. 49%) and improved DFS (51% vs. 31%) at 18 months in comparison to historical controls treated with the LALA-94 protocol. An Italian study also reported 5-year OS of 38% and DFS of 39% with imatinib combined with chemotherapy and again these results were significantly superior to a historical cohort receiving chemotherapy alone.¹²² In the large UKALL/ECOG2993 trial investigators reported an improved post-induction CR rate with imatinib, improved 4 year OS, EFS and a considerable reduction in relapse risk in the imatinib cohort.¹²³ Lastly, The M.D. Anderson group also combined imatinib with their standard hyper-CVAD protocol and reported CR rates of 93% as well as results that were substantially superior to their retrospective results with chemotherapy.¹²⁴

Second and third generation TKI's have also been assessed in Ph+ ALL.¹²⁵⁻¹²⁸ Kim et al evaluated the outcomes of Nilotinib with multiagent chemotherapy for adult patients with newly diagnosed Ph+ve ALL. After achieving CR, subjects received either 5 courses of consolidation, followed by 2-year maintenance with nilotinib, or allo-HCT. Amongst the 90 evaluable subjects the CR rate was 91%, the 2-year RFS was 72% and the 2-year OS was 72%. Unlike nilotinib, dasatinib has the ability to penetrate the CNS. Single agent dasatinib is associated with short-term cytogenetic remission and median relapse free survivals of only 3.3 months. Studies of dasatinib in combination with chemotherapy, however, have been associated with excellent response rates approaching 100% with minimal toxicity.^{72, 125} Ponatinib was evaluated in Ph+/BCR-ABL+ by Jabbour and colleagues for patients up to age 60 with previously untreated Ph +ve ALL. Ponatinib 45 mg was given daily for the first 14 days of cycle 1 then continuously each subsequent cycle of hyper-CVAD. Patients in complete remission received maintenance with ponatinib 45 mg daily with vincristine and prednisone monthly for 2 years followed by ponatinib indefinitely. The 2-year EFS rate was 81% (95% CI 64-90) for the 37 patients enrolled in the study.¹²⁸

Several investigators have combined TKI's with paediatric based regimens used for the treatment of adult patients. Thyagu et al. evaluated the outcomes of 32 ALL patients age 18-60 with Philadelphia positive ALL treated between 2001 and December 2008 with imatinib. Ninety-four percent of patients (94%) achieved a CR and, of the 28 patients proceeding to intensification therapy, 16 received a HSCT. The 3-year OS was 56% in the transplanted group vs. 50% in the non-transplanted group.¹²⁹ They also noted increased rates of peripheral neuropathy, ileus, myopathies, deconditioning, infections and abnormal liver enzymes in a high proportion of patients. Therefore, a number of modifications were made to the original DFCI protocol.¹²⁹ Using an unmodified DFCI protocol,

DeAngelo et al. reported similar results amongst 18 Ph +ve patients treated with imatinib, 11 of whom went on to transplant. The 4 year DFS was 54% and 4 year OS was 53%.⁹⁵ Martell et al. also treated 16 BCR-ABL positive patients aged 62 – 75 with a modified DFCI protocol together with imatinib. The CR rate was 81% with an induction mortality of 19% and the estimated 5-year OS was 47.3% for the BCR-ABL1+ patients.¹⁰⁹

Monotherapy with TKI has been explored in several studies particularly in elderly patients, who had an extremely poor outcome with chemotherapy alone. Ottmann et al evaluated imatinib monotherapy in 27 patients older than 55 years of age, and observed CR in 26 patients and a partial remission in the remaining patient.¹³⁰ Vignetti et al. treated patients aged 61 to 83 years with Ph-+ ALL with a 45-day induction of imatinib 800 mg daily plus prednisone (40 mg/m² daily). Post-remission therapy was not specified. All 29 assessable patients (100%) experienced a CR. At 12 months, the OS and DFS probabilities were 74% and 48%, respectively.¹³¹

The French GRAALL group conducted a large randomised controlled trial comparing a reduced intensity induction with imatinib, vincristine and dexamethasone (Arm A) to standard imatinib/hyper-CVAD A part (Arm B) in 268 adults with Ph+ve ALL up to age 60; both arms then received a second cycle with Hyper-CVAD B part.¹³² The CR rate was higher in arm A than in arm B (98% vs 91%), mainly related to a lower induction death rate in Arm A, whereas the MMoIR rate was similar in both arms (66% vs 64%). The OS was superior in the patients that subsequently proceeded to allogeneic HSCT; however, on subgroup analysis, patients who had achieved MRD negativity (defined as a >4 log reduction in BCR-ABL transcripts by PCR) by the end of the second induction cycle had a similar RFS with or without allogeneic HSCT. In contrast patients who were MRD positive at that timepoint had a significantly better RFS with allogeneic HSCT, compared to those who were not transplanted. Therefore, MRD assessment with this regimen could be used to help identify a high-risk cohort for whom HSCT was beneficial.

Foa et al. evaluated a similar regimen consisting of dasatinib (70 mg twice daily for 84 days) together with prednisone 60 mg/m² daily for 32 days plus two doses of intrathecal methotrexate in untreated patients with Ph +ve ALL.¹²⁵ Post remission therapy was not defined with two patients receiving no further therapy, 19 continuing on TKI only, 10 receiving intensive chemotherapy with TKI, 4 having an autograft and 18 receiving an allogeneic HSCT. Overall, 53 patients aged 24 – 76 were treated. A CR rate of 100% was seen with 92.5% by day 22 and no deaths occurred during induction. Of the patients that had MRD measured by PCR 10 achieved levels lower than 10⁻³ and 8 had a complete molecular remission. Twenty-three patients relapsed after completing induction with 12/17 relapsing patients showing a T315I mutation. This trial demonstrated impressive remission rates for dasatinib and steroids only but at the same time underscored the importance of adding intensive chemotherapy and/or HSCT to maintain durable remissions.

The MD Anderson group evaluated the use of ponatinib + Hyper-CVAD chemotherapy in fit patients with BCR-ABL+ ALL.¹³³ The 3-year EFS of 69% and OS of 84%, without transplant, were significantly superior to a historical group that had received dasatinib + Hyper-CVAD. These results suggest that using ponatinib with intensive chemotherapy upfront may potentially circumvent the need for transplant in CR1 for most patients. The PHALLCON study, a randomized trial comparing imatinib vs. ponatinib combined with chemotherapy, reported a higher MRD negative rate with ponatinib (34.4% vs 16.7%, $p=0.002$), associated with a superior event-free survival.¹⁶⁶

More recently the Italian GIMEMA group reported on a chemo-free regimen using dasatinib + blinatumomab (D-ALBA).¹³⁴ The CR rate was 98%, with 70-80% eventually achieving a complete molecular response; at a median follow-up of 18 months, the OS was 95% and DFS 88%. The MD Anderson group is currently using a combination of ponatinib + blinatumomab for 4 cycles, followed by ponatinib maintenance therapy, as their standard frontline regimen; the CR rate was 100% and 86% achieved a complete molecular response¹⁵⁴. At a median follow-up of 29 months, the EFS was 78% and OS 88%¹⁶³. The Italian GIMEMA group reported results of a randomized trial comparing blinatumomab + ponatinib to chemotherapy + TKI¹⁶⁴. At a median follow-up of 23.4 months, the EFS in the blina-ponatinib arm was 90% and OS was 94%; these results were significantly superior to the cohort that received chemotherapy + TKI. Less than 20% of patient in this study underwent HSCT. Notably, 70% of blina-ponatinib treated patients achieved *BCR-ABL* MRD negativity after 2 cycles of blinatumomab. In addition, patient who were later crossed over from chemo-TKI to the blina-ponatinib arm, mostly on the basis of residual MRD positivity, had a comparable OS to those starting on blina + ponatinib upfront. While these results are very promising, the combination of blinatumomab + TKI is not currently approved as upfront therapy for BCR-ABL+ ALL. However, it may be considered in patients who become unfit for post-remission intensification chemotherapy, or who are MRD positive post-induction by flow +/- Clonoseq and decline transplant.

Role of HSCT in Patients with Ph/BCR-ABL Positive ALL:

The UKALLXII/ECOG 2993 study evaluated the outcomes with HSCT in Ph+/BCR-ABL+ patients younger than 55 years of age achieving complete remission with an adult ALL protocol. Of the 267 patients, 76 (28%) proceeded to HSCT in first CR (45 with cells from a sibling and 31 with cells from a MUD) whereas 86 received chemotherapy alone. The median EFS for all 267 Ph+ patients was 9 months and the median OS was 13 months. At 10 years, OS was 39% for sib HSCT, 31% for MUD HSCT, and 13% for chemotherapy. Comparing the outcome after any HSCT with the outcome after chemotherapy alone, OS, EFS, and RFS were all significantly superior for patients receiving any HSCT over those receiving chemotherapy alone. Whereas the leading cause of death in chemotherapy treated patients was relapse, the leading cause of death after transplantation was TRM, which was 27% after sib HSCT and 39% after MUD HSCT.³¹

Limited information is available comparing adult Ph+ patients receiving a paediatric protocol with those undergoing an HSCT. Thyagu et al. treated 32 patients with Ph+ ALL with DFCl protocol

together with imatinib. Of the 28 patients proceeding to intensification therapy, 16 underwent HSCT. The 3 year OS was 56% in the transplanted group and 50% in the non-transplanted group.¹²⁹ Recent studies in the pediatric setting noted that children receiving intensive multidrug chemotherapy with imatinib had a survival higher than 80% compared to 35% in historical controls, and even better than related or unrelated HSCT (>60%). In the recent US Children's' Oncology Group study, the outcomes at 3 years were not significantly different for those treated with chemotherapy plus imatinib compared with those assigned to HSCT.¹³⁸ However, limited patient numbers precluded rigorous subgroup analysis.

Recent studies in adults are also demonstrating the impact of molecular status on relapse risk in Ph+ ALL. The MD Anderson Cancer Center¹³⁹ found that molecular positivity at a variety of time points was associated with a significantly higher cumulative incidence of relapse. The French GRAAPH study¹³² found that the benefit of HSCT in CR1 was restricted to patients who were molecularly positive post-induction chemotherapy. On subgroup analysis, patients who had achieved MRD negativity (defined as a >4 log reduction in BCR-ABL transcripts by PCR) by the end of the second induction cycle had a similar RFS with or without HSCT. In contrast patients who were MRD positive at that timepoint had a significantly better RFS with HSCT, compared to those who were not transplanted. Therefore, MRD assessment with this regimen could be used to help identify a high risk cohort which benefitted from HSCT.

However, there are differences between MRD assessments by *BCR-ABL* PCR and Immunoglobulin gene rearrangements by NGS (IgR). A study from the French GRAAPH group using TKI plus chemotherapy found that IgR MRD was predictive of DFS but *BCR-ABL* PCR was not; this was confirmed on multivariate analysis.¹⁶⁷ Furthermore, only those who were MRD positive by IgR benefitted from HSCT, while those who were IgR negative but *BCR-ABL* positive did not benefit. A more recent study from MD Anderson Cancer Center confirmed that *BCR-ABL* positivity by PCR conferred no prognostic information in those who were MRD negative by IgR using ClonoSEQ.¹⁶⁸ Taken together, these data suggest that HSCT eligibility should be determined by evidence of a residual lymphoblast population by MRD and not by *BCR-ABL* positivity alone.

Recommendations for BCR-ABL Positive ALL:

All patients with Ph/*BCR-ABL*+ve ALL should receive a TKI combined with chemotherapy. Either imatinib (600- 800 mg daily) or dasatinib (100 mg daily) may be used as first line therapy. Patients intolerant to imatinib should be switched to another TKI such as dasatinib; dasatinib may be preferred for patients with CNS disease due to its excellent CNS penetration. Patients with documented T315I *BCR-ABL* mutations, or those refractory to or progressing on, a 2nd generation TKI, should be treated with ponatinib.

Fit *BCR-ABL*+ve ALL patients should be treated with a TKI combined with induction and post-remission chemotherapy. Given studies showing higher remission rates and decreased mortality using corticosteroids, TKI + vincristine during induction, this combination is recommended as initial induction therapy (see Appendix F); however, such patients require additional intensive chemotherapy +/- HSCT to maintain a durable remission.

Given data suggesting increased toxicity of asparaginase and vincristine with TKI, asparaginase should be deleted, and vinblastine substituted for vincristine, in the post-remission phases. Patients above age 65, particularly, those with major co-morbidities, poor performance status or ineligible for SCT should be treated with steroid and TKI +/- vincristine or vinblastine. Post induction therapy should be individualized based upon patient tolerance. Patients not transplanted should continue TKI indefinitely.

BCR-ABL monitoring by quantitative RT-PCR should be performed in all patients, post-induction and then every 3 months. Patients with inadequate response or loss of response should be switched to a second or third generation TKI as indicated and, depending on circumstances, may require switching from chemotherapy to blinatumomab. MRD should also be assessed by a technique to evaluate for a residual lymphoblast population. Although IgR MRD assessment is the optimal technique, this assay is not routinely available in Alberta; therefore, bone marrow MRD assessment by multiparameter flow cytometry should be used; if inadequate or indeterminate, the sample should be sent for IgR testing, as this is important in determining prognosis and need for HSCT.

If patients are MRD positive by flow cytometry after the Chalandon induction phase, blinatumomab should be given with an aim to achieve MRD negativity. Patients who are unable to tolerate intensification chemotherapy may be considered for the combination of blinatumomab x 5 cycles + TKI, followed by maintenance TKI therapy.

Although allogeneic HSCT remains the standard post-remission approach for high-risk patients with *BCR-ABL* positive ALL, patients who achieve early MRD negativity post-induction +/- blinatumomab may be continued on post-induction chemotherapy + TKI without a transplant; these patients should continue with indefinite TKI and regular MRD monitoring. If *BCR-ABL* positive by PCR but MRD negative by flow cytometry, molecular MRD testing by IgR (e.g. Clonoseq^R) should optimally be performed. If negative by Clonoseq, patients may be continued on treatment without transplant. However, if MRD positive by flow or Clonoseq, patients should be referred for HSCT if otherwise eligible. Consideration should be given to switching to a more potent TKI such as dasatinib or ponatinib in these MRD+ patients. Furthermore, patients with subsequent recurrence of MRD detectable disease, or with a significant rise in transcript levels, should also be referred for transplant. For patients who are MRD positive by flow and/or IgR, and will not be proceeding to HSCT, or those intolerant to further chemotherapy, consideration should be given to switching to blinatumomab +

ponatinib or other TKI, followed by maintenance TKI, in an attempt to achieve a sustained MRD negative remission and prevent relapse.

E. CNS Prophylaxis and Treatment

CNS involvement at the time of presentation is uncommon in adults with ALL being reported in 5% to 7% of patients.¹⁴¹ Before the use of central nervous system (CNS) prophylaxis, the CNS was the most frequently reported site of initial recurrence in children with ALL, accounting for up to 75% of cases.¹⁴¹ Similarly, amongst adults with ALL, CNS recurrence occurs in approximately 30% of those in a hematological remission.¹ Therefore, effective CNS prophylaxis is mandatory in all patients.

Standard approaches include the use of repeated (12) doses of intrathecal (IT) chemotherapy. This has been demonstrated in many studies to reduce the risk of CNS relapse to 10% or less. Although many protocols use triple intrathecal chemotherapy with methotrexate, cytarabine and corticosteroids, a recent pediatric randomized study did not show any difference in CNS relapse rates between this approach and single-agent methotrexate.¹¹²

A baseline LP is required to rule out CSF disease at diagnosis. If positive, the usual approach is to administer intrathecal chemotherapy twice weekly until the CSF has been adequately cleared (as evidenced by 3 consecutive negative results). Although the standard cerebrospinal fluid (CSF) diagnostic approach consists of morphologic analysis of a cytospin preparation, studies have shown that flow cytometry of CSF provides greater sensitivity,¹¹³ and may thus be a more reliable indicator of blast clearance.

Aur et al. published the results of St. Jude Total Study V in 1971 demonstrating that 2,400 cGy cranial radiation and five doses of intrathecal methotrexate greatly diminished CNS relapse resulting in the first cures of childhood ALL.¹⁴² Subsequently, widespread incorporation of CNS prophylaxis led to the largest single “step up” in 10-year survival from approximately 20% to 60% among those diagnosed from 1970 to 1972 versus 1972 to 1975.¹⁴² Given the significant risk of CNS relapse current adult and pediatric protocols incorporate CNS prophylaxis with both systemic and intrathecal chemotherapy and/or radiation.

Cranial irradiation is an effective form of CNS-directed treatment, but its effectiveness is offset by substantial rates of secondary neoplasms, endocrinopathies, growth impairment, neurocognitive dysfunction, and neurotoxic effects. Amongst the pediatric population, Pui et al. found that prior cranial radiation was associated with a 20.9% cumulative risk of second neoplasms at 20 years in addition to a higher mortality and a greater likelihood of being unemployed when compared to an age matched general population.¹⁴² Subsequently, multiple trials compared CNS prophylaxis using intrathecal chemotherapy and/or intravenous methotrexate with cranial radiation. These trials demonstrated the efficacy of IT/IV therapy without cranial radiation leading to use of cranial irradiation

for patients at especially high risk of CNS relapse and elimination of cranial radiation for infants or very young children, irrespective of their presenting features Jeha, 2009 #199. More recently, in the St Jude Total XV and Dutch Childhood Oncology Group acute lymphoblastic leukaemia-9 protocols cranial irradiation is replaced by triple intrathecal chemotherapy with methotrexate, hydrocortisone, and cytarabine for all newly diagnosed patients. The 5 year cumulative risk of isolated CNS relapse was 2.7% with the St Jude and 2.6% with the Dutch Childhood Oncology Group protocol similar to the relapse rates observed with prophylactic cranial irradiation (1.5–4.5%). In the largest study to date Vora and colleagues¹⁴³ obtained data on 16623 patients aged 1 to 18 years old treated between 1996 and 2007 by 10 cooperative groups. In their analysis cranial radiation was associated with a reduced risk of relapse but only in patients with overt CNS disease at time of presentation. In other patients there was no difference in CNS relapse between those that received and did not receive cranial radiation. These data suggest that, in the context of a pediatric protocol prophylactic cranial irradiation can be safely omitted in patients in the context of effective intrathecal and systemic chemotherapy. This is particularly the case if high-dose intravenous methotrexate, which has good CNS penetration, is used. However, if evidence of fixed leptomeningeal disease is present based on the presence of focal neurologic symptoms and corresponding MRI findings, CNS radiotherapy is indicated as intrathecal chemotherapy alone is usually insufficient.

Recommendations for CNS Prophylaxis and the Role of Cranial Radiation:

All patients should receive at least 12 doses of intrathecal chemotherapy. Unless contraindicated, high-dose methotrexate should also be given, owing to its high CNS penetration. If high-dose methotrexate is not used, 15 doses of intrathecal chemotherapy are recommended.

Cranial irradiation may be omitted from CNS prophylaxis in patients receiving a pediatric protocol such as the DFCI, unless there is evidence of fixed intracranial disease at presentation on MRI.

F. Supportive Care

Supportive care remains an important aspect of the care of the ALL patient throughout all phases of treatment. All patients should be transfused packed red blood cells as per institutional guidelines and particularly for symptomatic anemia. Similarly, platelets should be transfused to maintain platelet counts $> 10 \times 10^9/L$. All patients receive prophylaxis, and if indicated, treatment for tumour lysis syndrome with allopurinol and/or rasburicase during induction therapy. Disseminated intravascular coagulation should be treated aggressively with clotting factor replacement. Patients with signs and symptoms of febrile neutropenia should be managed with broad spectrum antibiotics and intensive care support as necessary. As corticosteroids may mask fevers in such patients, broad spectrum antibiotics should be instituted for clinical suspicion of sepsis (e.g. unexplained hypotension) even in

the absence of fever. Antifungal prophylaxis against *Candida* is recommended during induction due to the risk of *Candida* septicemia.

Clinicians should be continuously aware of both the short- and long-term consequences of potential toxicities associated with specific agents used in ALL and use prevention, treatment or dose adjustment as necessary:

1. Corticosteroids may lead to hyperglycemia or gastrointestinal reflux/gastritis in the acute setting. Patients are also at risk for osteoporosis and osteonecrosis (avascular necrosis, AVN) with long-term use. Patients should be treated with gastric protective agents (e.g. PPI), calcium, vitamin D and bisphosphonates. Patients developing persistent pain in hips or other joints should have an MRI scan to exclude AVN.
2. Asparaginase has been associated with hypersensitivity reactions, hyperglycemia, coagulopathy, hepatotoxicity, and/or pancreatitis. Liver function tests should be performed regularly and patients should be monitored for clinical signs/symptoms of pancreatitis. Triglyceride levels should also be monitored as severe hypertriglyceridemia may be seen and could potentially increase the risk of pancreatitis. Severe hypertriglyceridemia (e.g. > 10 mmol/L) would warrant treatment with fenofibrate; if ineffective, omega-3 fatty acids may be added. The development of pancreatitis requires discontinuation of asparaginase due to the high risk of recurrence. Grade 2 or higher liver toxicities warrant consideration of a dose reduction with subsequent cycles (see below for monitoring).
3. Anticoagulation prophylaxis with adjusted dose low-molecular weight heparin during the intensification phase of the DFCl protocol has been associated with a reduced risk of VTE¹⁴⁴ and should be considered due to the high risk of VTE (25-30%²⁰); patients should be closely monitored for clinical signs of VTE. If a VTE is diagnosed, full-dose anticoagulation should be instituted, and the asparaginase can be resumed after several weeks.
4. Hypersensitivity reactions should be carefully assessed to exclude infusion type reactions. If unclear, a serum asparaginase level should be obtained 3-7 days later to confirm rapid clearance of drug.¹⁴⁵ If confirmed based on clinical suspicion and lack of detectable asparaginase, the patient should be switched to Erwinia asparaginase which should be given 3x/week due to its short half-life.¹⁴⁶
5. Therapeutic drug monitoring: Silent inactivation of asparaginase, due to rapid clearance by antibodies, may also occur which could compromise treatment efficacy. Because of this, it is recommended that all patients have a trough serum asparaginase level drawn at the end of the first cycle of intensification therapy (i.e. days 19-22), targeting a level ≥ 1.0 U/L. A trough level should be repeated at cycle 6, or anytime if suspected based on surrogate markers (e.g. normal LFT's and fibrinogen levels). If the trough level is < 0.1 U/L, an asparaginase level should also be

repeated at day 3-7 post-dosing with the next cycle; if still <0.1 U/L, this would be consistent with silent inactivation and warrants a switch to Erwinia (van der Sluis et al 2016). Asparaginase levels may also be useful in de-escalating doses to manage or prevent severe toxicity. Standardized approaches are lacking, although some centres are now de-escalating the dose if the trough level is >0.3 U/L. Any dose reduction should be followed by a repeat trough asparaginase level with the next cycle.

The current drug used for patients with sensitization or silent inactivation is Crisantaspase, which is a recombinant form of Erwinia asparaginase. It should be given 3x per week due to its short half-life. The standard dosing is 25 mg/m² qMon & Wed, and 50 mg/m² qFriday, given IM for 9 doses per cycle during intensification.

6. Vincristine can cause neuropathies including peripheral neuropathy and ileus. Careful attention to a bowel regimen to prevent severe constipation (e.g. PEG +/- sennosides) should be done. Patients with progressive peripheral neuropathy should be switched to vinblastine (6 mg/m² to a maximum of 10 mg/dose).
7. Other drugs: Doxorubicin may lead to cardiomyopathy while methotrexate and 6-mercaptopurine can lead to hepatotoxicity. Patients requiring tyrosine kinase inhibitors may encounter a variety of general and TKI specific side-effects.
8. Antimicrobial prophylaxis: Patients are severely immunocompromised and are at high risk of serious infections, including neutropenic sepsis, *pnueumocystis jiroveci* pneumonia (PJP), viral infections (HSV or VZV reactivation, severe outcomes with influenza or COVID-19 infection), oropharyngeal Candidiasis, etc. Filgrastim should be used as needed for severe neutropenia during intensification phases. PJP prophylaxis (SMX-TMP, dapsone or inhaled pentamidine) and valacyclovir should be used. Patient should be strongly encouraged to undergo vaccination against influenza and COVID-19, and confirmed infection should be treated in its early stages with appropriate antiviral therapy to prevent severe outcomes.

Follow-Up

For patients with ALL the highest risk of relapse remains within the first two years following completion of chemotherapy. Patients should have regular blood work for the first 2-3 years and every three months thereafter until 5 years. Patients with concerning laboratory features or clinical signs and symptoms for ALL relapse should be evaluated with repeat bone marrow studies.

G. Treatment of Relapsed ALL

Adult ALL patients experiencing hematologic relapse have a poor prognosis with conventional chemotherapy salvage regimens. CR2 rates have been in the 30-50% range. Second remissions are invariably brief unless followed by allogeneic HSCT, and OS is in the 10-20% range.^{147, 148} Recent studies have demonstrated the superiority of antibody-based therapies for relapsed patients with B-ALL. Blinatumomab, a BiTE antibody construct described earlier (see MRD Section), was evaluated in the Phase III randomized TOWER trial¹⁵⁶. Adult B-ALL patients with relapsed (CR1 < 12 months or $\geq$ CR2) or refractory disease were randomized to receive either blinatumomab for 2 cycles, followed by up to 3 consolidation cycles, or conventional salvage chemotherapy. The CR rate was higher with blinatumomab (44% vs. 25%, $p=0.001$), and OS was significantly longer in the blinatumomab arm (7.7 months vs. 4 months, $p=0.01$). Responses in the blinatumomab arm were influenced by tumour burden: The CR rate was 65% in those with < 50% bone marrow blasts, vs. 34% in those with $\geq$ 50% BM blasts; nevertheless, CR rates were higher in both subgroups as compared with the chemotherapy arm. Although this study only included patients with BCR-ABL negative ALL, a subsequent study demonstrated a 36% CR rate in patients with relapsed/refractory BCR-ABL+ B-ALL, all of whom had failed second or later generation TKI's.¹⁴⁹

Inotuzumab ozogamicin is an anti-CD22 antibody conjugated to the toxin calicheamicin. The immunoconjugate is internalized into CD22+ B-cells, followed by release of the calicheamicin, which induces DNA strand breaks. The INO-VATE trial was a Phase III randomized study in patients with relapsed/refractory CD22+ B-ALL.¹⁵⁰ Patients were randomized to receive inotuzumab or conventional salvage chemotherapy. The CR rate was significantly higher in the inotuzumab arm (81% vs. 29%, $p<0.001$); furthermore, nearly all CR's in the inotuzumab group were MRD negative. The PFS in the inotuzumab group was also significantly longer (5 mos vs. 1.8 mos, $p<0.001$), and the OS was also longer (7.7 mos vs. 6.7 mos, $p=0.04$). CR rates with inotuzumab were not influenced as much by tumour burden (86.7% for those with <50% BM blasts, vs. 78% for those with $\geq$ 50% BM blasts). Notably, this study included patients with BCR-ABL+ ALL, where a 79% CR rate was reported.

In addition to being more effective, both antibody drugs were well tolerated. The major toxicities of blinatumomab included cytokine release syndrome and neurologic toxicity, both of which were usually grade 1-2 and treated successfully with corticosteroids. The major toxicities of inotuzumab were nausea, febrile neutropenia and veno-occlusive disease (VOD/SOS) of the liver. The latter was a particular issue in patients who received >3 cycles and in those who subsequently proceeded to allogeneic HSCT using a dual alkylator conditioning regimen.

For patients with relapsed/refractory T-ALL, there are currently no available antibody-based therapies outside of clinical trials. Conventional salvage chemotherapy, using a non-cross resistant regimen (e.g. Hyper-CVAD), may be used, or nelarabine. The latter is a prodrug of ara-G which is converted to

ara-GTP, after which it is then incorporated into DNA, resulting in cytotoxicity. It has demonstrated single agent activity in relapsed/refractory T-ALL, with a 31% CR rate and 41% ORR.¹⁵¹ However, responses are not durable, and require subsequent allogeneic HSCT if treated with creative intent. Major toxicities of nelarabine include myelosuppression and neurotoxicity. Neurotoxic effects may be either central or peripheral, and may be severe and irreversible.

Recommendations for Relapsed ALL:

Based on the two pivotal TOWER and INO-VATE trials, patients with relapsed or refractory BCR-ABL negative B-ALL should be treated with either blinatumomab or inotuzumab as salvage therapy. Although there are no clear recommendations with respect to the choice of agent, inotuzumab would generally be preferred in patients with higher disease burdens (> 50% BM blasts), based on higher responses rates in this group. In patients with lower disease burden, blinatumomab will be preferred for patients who are intended to proceed to subsequent allogeneic HSCT, due to the risk of VOD/SOS with inotuzumab.

For patient who receive inotuzumab with an intention to proceed to HSCT, patients should optimally not receive more than 2 cycles, and dual alkylator HSCT conditioning regimens should subsequently be avoided. It should also not be used within 40-50 days prior to HSCT, as this may increase the risk of VOD post-HSCT. Conventional chemotherapy or blinatumomab may be preferred in patients who are at risk of VOD/SOS (patients who are early post-HSCT or have pre-existing liver issues).

Patients with relapsed BCR-ABL positive B-ALL on imatinib may be reinduced with a second generation TKI such as dasatinib + chemotherapy. Mutational analysis should be performed at relapse and, if a T315I mutation is detected, ponatinib should be used. Those failing a second generation TKI, should be treated with either inotuzumab or blinatumomab, optimally combined with ponatinib.

Patients with relapsed/refractory T-ALL should receive either salvage chemotherapy with a non-cross resistant regimen (e.g. Hyper-CVAD) or nelarabine.

Regardless of salvage therapy, subsequent relapse is inevitable unless the patient proceeds to allogeneic HSCT or CAR T-cell therapy (see below).

H. CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy is a treatment in which T lymphocytes are removed from a patient via apheresis, transfected *ex vivo* with a gene rendering them immunogenic against certain cancer cells, grown and subsequently reinfused into the patient. The activated T-cells then

circulate, attack and kill the cancer cells. This treatment has demonstrated considerable activity in patients with relapsed and refractory B-ALL.

Most studies to date have utilized anti-CD19 CAR T-cells. Tisagenlecleusel is the first such therapy to be approved in children and young adults up to age 25 with relapsed/refractory B-ALL. Complete remission rates of 81% were reported,¹⁵² with a one-year event-free survival (EFS) of 50%, in a cohort of multiple relapsed patients, many of whom had previously received allogeneic HSCT. Another study of 53 multiply relapsed and refractory B-ALL patients, including many older patients age 30-70 years, from Memorial Sloan Kettering Cancer Center (MSKCC) using a similar anti-CD19 CAR T-cell product, demonstrated an 83% CR rate, a median EFS of 6.1 months and OS of 12.9 months (Park et al, 2021). In this study, patients with a low disease burden (defined as <5% BM blasts) at the time of CAR T infusion had a superior EFS and OS as compared with those who had >5% BM blasts at time of infusion. The ZUMA-3 study, using a different anti-CD19 CAR T-cell product, reported a CR rate of 83% and a median remission duration of 17.6 months¹⁶¹. This product, brexucaptogene autoleucel (Brexu-cel)¹⁶², has now been approved by Health Canada for patients with relapsed/refractory B-ALL.

CAR T-cell therapy is associated with significant early toxicities, including cytokine release syndrome (CRS), sometimes requiring ICU support +/- tocilizumab, and neurotoxicity; patients therefore require close monitoring in the first two weeks. The MSKCC group¹⁵³ and others have reported that the severity of these toxicities is greater in patients with higher tumour burden at the time of CAR-T infusion.

There is increasing evidence that the tumour burden just prior to CAR-T therapy influences outcomes. Specifically, patients with <5% marrow blasts have had superior outcomes, while high tumour burden is associated with higher relapse rates post-CAR-T.^{172,173,175} Patients with TP53 mutations have also been reported to have inferior outcomes.¹⁷⁶

CAR T-cell therapy has become available in Alberta as of 2021, in both Edmonton and Calgary, using both commercial and local investigational products. It is currently being used for patients who have failed at least two different treatment regimens; however, the field is rapidly evolving, and it is likely that it will be evaluated at earlier stages of disease. As some patients relapse with CD19-negative disease, other studies are investigating the use of dual anti-CD19/CD22 CAR-T products.

Potential candidates for this treatment should be referred early for apheresis, prior to administering salvage immunosuppressive chemotherapy, so as not to negatively interfere with the quality of the apheresis product. Most patients will need some bridging cytoreductive therapy. The latter has a dual purpose: (1) to prevent clinical deterioration while the CAR T product is being prepared, and (2) to reduce the disease burden, potentially reducing the toxicity of the procedure and the risk of subsequent relapse. Optimal cytoreductive strategies are unclear; depending on the patient, it may

include non-intensive chemotherapy, inotuzumab or blinatumomab. Inotuzumab should be avoided in patients at higher risk of VOD/SOS, including those who are early post-HSCT or who have pre-existing liver disease. There is also evidence that prior use of inotuzumab may be associated with inferior outcomes post-CAR-T therapy¹⁷⁴; while not contraindicated, some experts recommend keeping the use of this to a minimum (not more than one cycle), as bridging therapy. Blinatumomab, while also not contraindicated, could potentially increase the risk of emergence of a CD19 negative subclone, although in practice this occurs in less than 10% of relapsed cases.

The need for HSCT post-CAR-T therapy is controversial. In the ZUMA-3 study, the use of post-CAR-T HSCT was not associated with better outcomes.¹⁷⁵ In contrast, other studies have shown superior outcomes if patients proceed to subsequent HSCT.^{176,177} Patients who remain MRD positive post-CAR-T, those with early loss of CAR-T within the first 3 months¹⁷⁶ or have early loss of B-cell aplasia¹⁷², have inferior outcomes and should proceed to HSCT. In contrast, older patients (>age 60), patients who have relapsed post-HSCT or those with MRD negativity prior to CAR-T have better outcomes with CAR-T therapy alone and may not need subsequent HSCT.

Recommendations for CAR-T:

CAR T-cell therapy is indicated for fit patients with B-ALL who have relapsed after allogeneic HSCT, are not otherwise candidates for HSCT, or who have refractory disease; this may include those with persistent MRD positivity despite both chemotherapy and blinatumomab. Early referral to the centre's Cellular Therapy Program is recommended. Patient should not receive salvage T-cell depleting immunosuppressive therapies such as corticosteroids or cyclophosphamide until after apheresis, so as not to impair the quality of the collection. Following apheresis, bridging/cytoreductive therapy should be given, particularly for high tumour burden or rapidly progressive disease, with an aim to control disease-related complications and reduce the overall tumour burden, preferably to CR if possible, while avoiding excessive treatment-related toxicities.

I. Future directions

The treatment landscape of ALL has undergone major changes in the past 5 years, and it is likely that further changes will occur as new information becomes available.

For BCR-ABL negative ALL, less intensive induction strategies are being investigated in older adults, in an attempt to reduce the substantial toxicities and risk in these patients. For B-ALL, this includes the addition of antibody-based treatments (inotuzumab and blinatumomab) to reduced intensity regimens, or alone. For T-ALL, the addition of nelarabine to standard chemotherapy has been found to be of benefit in children, and is being investigated in adults. Other novel agents such as venetoclax and brexuciclib and also being evaluated, and have shown activity in ETP-ALL. For *BCR-ABL*-like B-

ALL, the addition of targeted agents such as dasatinib and ruxolitinib is being evaluated, although results with the latter have been disappointing to date. Finally, the subcutaneous administration of blinatumomab has shown very promising activity in early trials in relapsed/refractory B-ALL, with CR rates in excess of 80%, and may eventually supplant the IV formulation. Other bispecific antibody constructs (e.g. MK-1045) have also shown encouraging early results and are in active clinical trials.

For *BCR-ABL* positive ALL, the combination of ponatinib with Hyper-CVAD chemotherapy has shown very favourable results, without transplant, compared with historical cohorts who had received first or second generation TKI's.¹³³ More intriguingly, chemo-free protocols, using blinatumomab combined with either dasatinib or ponatinib, have shown very encouraging results in early studies, as described.^{134,154} If successful, these may fundamentally change how these patients are treated in the future, and may render transplants unnecessary in most cases.

Dual CAR-T constructs, targeting both CD19 and CD22, are in clinical trials, and offer the promise of lowering relapse rates. Moreover, CAR-T therapies are being evaluated in earlier stages of the disease, after first relapse and in first CR for high-risk patients with MRD positive disease. This may, if successful, potentially replace the need for allogeneic HSCT for many patients, thereby eliminating the problems associated with GVHD. The use of CAR-T therapy for T-ALL has been much more challenging, but early studies are in progress.

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Appendix A: Princess Margaret Hospital Modified DFCI 91-01/AI.4 Protocol²⁰) for T-cell ALL patients aged <55-60 Years, Modified for Pegaspargase (see Appendix C for B-ALL)

Phase of Therapy	Time Period	Chemotherapy
Induction	28 Days	Vincristine 2 mg weekly, days 1, 8, 15 and 22 Prednisone 40 mg/m ² /day, days 1 –28 Doxorubicin 30 mg/m ² /dose, days 1 and 2 Methotrexate 4 g/m ² (8–24 h after doxorubicin) with leucovorin rescue on day 3 Pegaspargase 1000 U/m ² IV × 1 dose, day 12* IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg), days 1, 15, 29
CNS Therapy	3 Weeks	Vincristine 2 mg × 1 dose day 1 6-mercaptopurine (6-MP) 50 mg/m ² /day orally, day 1 -14 Doxorubicin 30 mg/m ² × 1 dose day 1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) twice weekly × 4 doses
Intensification	Every 3 weeks for 10 cycles (30 weeks)	Vincristine 2 mg, day 1 Dexamethasone 9 mg/m ² PO BID, days 1 –5 Doxorubicin 30 mg/m ² , day 1 of cycles 1-7(to a cumulative dose 300 mg/m ²) 6-MP 50 mg/m ² /day orally × 14 consecutive days Pegaspargase 1000 IU/m ² IV day 1* Methotrexate 30 mg/m ² IV, IM or PO weekly, on day 2, 9, and 16 on cycles 8-10 (after maximum doxorubicin dose completed). IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) start of a cycle every 18 weeks
Continuation	Every 3 weeks for 24 cycles (72 weeks)	Vincristine 2 mg, day 1 Dexamethasone dose reduced to 6 mg/m ² BID 6-MP 50 mg/m ² /day orally × 14 consecutive days Methotrexate 30 mg/m ² IV, IM or PO weekly days 1, 8 and 15 IT therapy consisting of methotrexate/cytarabine at start of a cycle every 18 weeks

* 750 U/m² in patients with BMI >30 or steatohepatitis; further adjustments as needed based on levels

Appendix B: Princess Margaret Hospital Modified DFCI 91-01/AI.4 Protocol²⁰ for BCR-ABL1 negative ALL patients aged >55-60 Years, Modified for Pegaspargase (see Appendix C for B-ALL Rx schema)

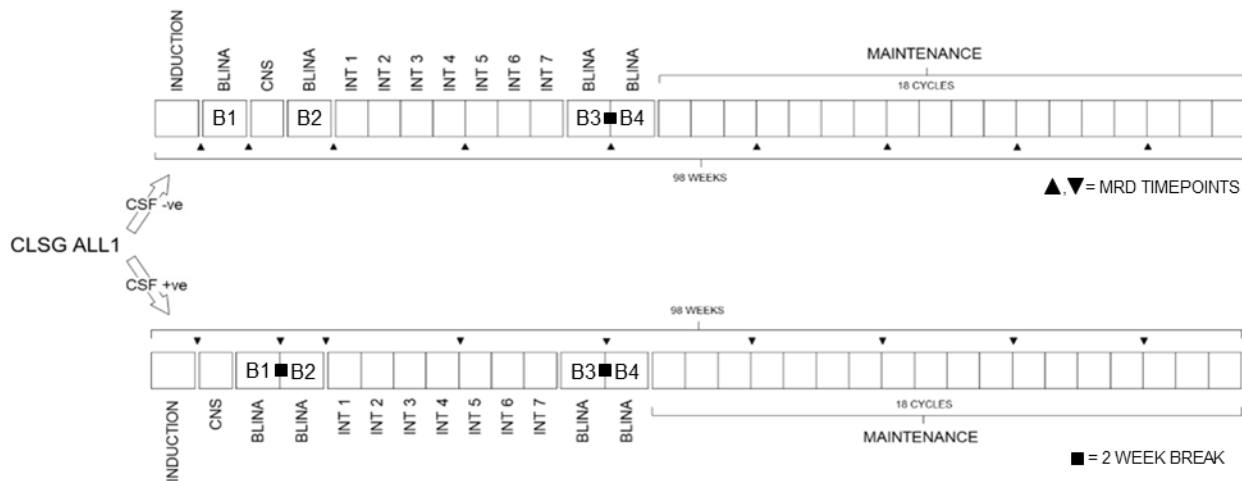
Phase of Therapy	Time Period	Chemotherapy
Induction	28 Days	Vincristine 2 mg weekly, days 1, 8, 15 Dexamethasone 40 mg, days 1-4, 9 –12 Doxorubicin 30 mg/m ² /dose, days 1 and 2 Methotrexate 40 mg/m ² , day 3 Pegaspargase 1000 U/m ² IV × 1 dose, day 4* IT Cytarabine 70 mg, day 1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg), days 15, 29
Edmonton Modified induction for B-ALL (2024)		Vincristine 2 mg weekly, days 1, 8, 15 Dexamethasone 40 mg, days 1-4, then 20 mg on Days 8 and 15 Doxorubicin 30 mg/m ² on Day 1 Pegaspargase 1000 U/m ² IV × 1 dose, day 4 IT therapy as above
Blinatumomab**	4 weeks	28 mcg daily CIVI x 28 days
CNS Therapy	3 Weeks	Vincristine 2 mg × 1 dose day 1 6-mercaptopurine (6-MP) 50 mg/m ² /day orally, × 14 consecutive days (day 1 -14) Doxorubicin 30 mg/m ² × 1 dose day 1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) twice weekly × 4 doses
Blinatumomab**	4 weeks	28 mcg daily CIVI x 28 days
Intensification	Every 3 weeks for 21 weeks	Vincristine 2 mg, day 1 Dexamethasone 6 mg BID, orally, days 1 –5 Doxorubicin 30 mg/m ² , day 1 6-MP 50 mg/m ² /day orally × 14 consecutive days Pegaspargase 1000 U/m ² IV day 1* IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) start of a cycle every 18 weeks
Blinatumomab**	4 weeks	28 mcg daily CIVI x 28 days
Blinatumomab**	4 weeks	28 mcg daily CIVI x 28 days
Continuation	Every 3 weeks for 54 weeks (B-ALL) or 72 weeks (T-ALL)	Vincristine 2 mg, day 1 Dexamethasone 6 mg PO BID days 1-5 6-MP 50 mg/m ² /day orally × 14 consecutive days Methotrexate 30 mg/m ² IV, IM or PO weekly days 1, 8 and 15 IT therapy consisting of methotrexate/cytarabine at start of a cycle every 18 weeks

* 750 U/m² in patients with BMI >30 or steatohepatitis; further adjustments as needed based on levels

** Only for B-ALL

Appendix C: Modified DFCl CLSG Protocol incorporating Blinatumomab, for BCR-ABL negative B-ALL.

1. Overall Protocol Schema:



Summary of changes to DFCl protocol:

- Four cycles of Blinatumomab added:
 - Cycle 1 given right after Induction phase
 - Cycle 2 given after CNS phase
 - Cycles 3 and 4 given after completion of Intensification phase, prior to starting Maintenance
- For patients with positive CSF at diagnosis, and/or evidence of fixed leptomeningeal disease, the CNS phase should be completed before starting cycle 1 of blinatumomab (lower chart)
- The number of post-remission chemo cycles is reduced:
 - Intensification cycles reduced from 10 to 7 (kept at 7 for older patients)
 - Maintenance cycles reduced from 24 to 18.
- MRD assessments added (may be reduced for patient achieving early MRD negativity)

DFCI CLSG Protocol incorporating Blinatumomab, for BCR-ABL negative B-ALL <age 55-60.

Phase of Therapy	Time Period	Chemotherapy
Induction	28 Days	Vincristine 2 mg weekly, days 1, 8, 15 and 22 Prednisone 40 mg/m ² /day, days 1 –28 Doxorubicin 30 mg/m ² /dose, days 1 and 2 Methotrexate 4 g/m ² , day 3 with leucovorin rescue starting on day 4 Pegaspargase 1000 U/m ² IV × 1 dose, day 12* IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg), days 1, 15, 29
Blinatumomab	4 weeks	28 mcg daily CIVI x 28 days
CNS Therapy	3 Weeks	Vincristine 2 mg × 1 dose day 1 6-mercaptopurine (6-MP) 50 mg/m ² /day orally, day 1 -14 Doxorubicin 30 mg/m ² × 1 dose day 1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) twice weekly × 4 doses
Blinatumomab	4 weeks	28 mcg daily CIVI x 28 days
Intensification	Every 3 weeks for 7 cycles (21 weeks)	Vincristine 2 mg, day 1 Dexamethasone 9 mg/m ² PO BID, days 1 –5 Doxorubicin 30 mg/m ² , day 1 of cycles 1-7 (to a cumulative dose 300 mg/m ²) 6-MP 50 mg/m ² /day orally × 14 consecutive days Pegaspargase 1000 IU/m ² IV day 1* IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) start of a cycle every 18 weeks
Blinatumomab		28 mcg daily CIVI x 28 days
Blinatumomab		28 mcg daily CIVI x 28 days
Continuation	Every 3 weeks for 18 cycles (54 weeks)	Vincristine 2 mg, day 1 Dexamethasone dose reduced to 6 mg/m ² BID 6-MP 50 mg/m ² /day orally × 14 consecutive days Methotrexate 30 mg/m ² IV, IM or PO weekly days 1, 8 and 15 IT therapy consisting of methotrexate/cytarabine at start of a cycle every 18 weeks

* 750 U/m² in patients with BMI >30 or steatohepatitis; further adjustments as needed based on levels

Appendix D: Princess Margaret Hospital Modified DFCI 91-01/AL.4 Protocol for Philadelphia Chromosome/BCR-ABL1 Positive Adult Patients Aged <55-60 Years¹²⁹

Phase of Therapy	Time Period	Chemotherapy
Induction	28 Days	Vincristine 2 mg weekly, days 1, 8 Vinblastine 10 mg, day 15 Prednisone 40 mg/m ² /day, days 1 –28 Doxorubicin 30 mg/m ² /dose, days 1 and 2 Methotrexate 4 g/m ² (8–24 h after doxorubicin) with leucovorin rescue on day 3 IT cytarabine 70 mg, day 1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg), days 15, 28 Imatinib 400 mg, days 1-16
CNS Therapy	3 Weeks	Vinblastine 10 mg × 1 dose day 1 6-mercaptopurine (6-MP) 50 mg/m ² /day orally, × 14 consecutive days (day 1 -14) Doxorubicin 30 mg/m ² × 1 dose day 1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) twice weekly × 4 doses Imatinib 400 mg daily, days 1-21
Intensification	Every 3 weeks for 21 weeks	Vinblastine 10 mg, day 1 Dexamethasone 9 mg/m ² / b.i.d., orally, days 1 –5 Doxorubicin 30 mg/m ² , day 1 of each cycle to a (cumulative dose 300 mg/m ²) 6-MP 50 mg/m ² /day orally × 14 consecutive days Methotrexate 30 mg/m ² i.v. or IM weekly, days 1,8 and 15 (after maximum doxorubicin dose completed). IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) every 18 weeks Imatinib 400 mg, days 1-21
Continuation	74 weeks	Vinblastine 10 mg, day 1 Dexamethasone 6 mg/m ² BID, days 1-5 6-MP 50 mg/m ² /day orally × 14 consecutive days Methotrexate 30 mg/m ² i.v. or IM weekly days 1, 8 and 15 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg) at start of a cycle every 18 weeks Imatinib 400mg, days 1-21
Long Term Maintenance		Imatinib 400-600 mg daily or other TKI

Appendix E: GRAAPH-2005 (aka Chalandon) Induction Protocol for Philadelphia Chromosome/ BCR-ABL1 Positive Adult Patients,¹³² with Modification for Older Patients

Phase of Therapy	Time Period	Chemotherapy
Prephase	7 Days	Prednisone 60 mg/m ² /day, days -7 to -1 IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg)
Cycle 1	4 Weeks	Vincristine 2 mg IV, days 1, 8, 15, 22 (for pts age ≥ 65, days 1 and 15 only) Dexamethasone 40 mg/d PO, days 1-2. 8-9, 15-16, 22-23 (for pts age ≥ 65, 20 mg/d) Imatinib 400 mg BID, days 1-28* IT therapy consisting of methotrexate (12mg)/cytarabine (50 mg)/hydrocortisone (15 mg), days 1, 8, 15 Filgrastim 5 µg/kg/d sc daily, days 15 until neutrophil recovery
Cycle 2 (only for pts < age 65)	3 Weeks	Methotrexate 1000 mg/m ² /d CIV over 24 hours, day 1 Cytarabine 3000 mg/m ² /d12h IV x 4 doses, days 2-3 (1500 mg/m ² for pts age 60-64) Imatinib 400 mg PO BID, days 1-14* Filgrastim 5 µg/kg/d sc daily, days 9 until neutrophil recovery
Should be followed by Intensification and maintenance therapy		(e.g. DFCI as per Appendix D or HyperCVAD + Imatinib)

*May substitute dasatinib 100 mg daily

Development and Revision History

This guideline was developed by a multidisciplinary working group comprised of members from the Alberta Provincial Hematology Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. The draft guideline was externally reviewed and endorsed by members of the Alberta Provincial Hematology Tumour Team who were not involved in the guideline's development, including surgical oncologists, radiation oncologists, medical oncologists, hematologists, nurses, pathologists, and pharmacists. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2016.

Maintenance

A formal review of the guideline will be conducted in 2023. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AHS, Alberta Health Services; CCA, Cancer Care Alberta

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Joseph Brandwein reports advisory board participation for Pfizer, Abbvie, Taiho Pharma, Jazz Pharma, BMS/Celgene, Avir Pharma, Astellas, and Amgen.

Derek Tilley has nothing to disclose.

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