Integration of Immunotherapy Into the Frontline Treatment of Acute Lymphoblastic Leukemia

Ajoy Dias, MD,[1] and Mark R. Litzow, MD[2]

[1]Immune Deficiency Cellular Therapy Program, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

[2]Division of Hematology, Mayo Clinic, Rochester, Minnesota

Corresponding author:
Mark R. Litzow, MD
Consultant, Division of Hematology
Professor of Medicine
Mayo Clinic, 200 1st Street SW
Rochester, MN 55905
Email: Litzow.Mark@mayo.edu

Abstract: Immunotherapy has transformed the treatment of acute lymphoblastic leukemia (ALL) over the past 2 decades, leading to excellent outcomes in adults and children. This is especially true in the setting of relapsed and refractory (R/R) disease, in which treatment outcomes formerly were dismal. Several immune therapies have shown efficacy and safety in the R/R setting, including monoclonal antibodies, bispecific antibodies, antibody-drug conjugates (ADCs), and chimeric antigen receptor (CAR) T-cell therapy. These new immunotherapy approaches have brought about a major paradigm shift in the treatment of R/R ALL, with very few long-term side effects in comparison with standard chemotherapy. These agents are now being used in patients with newly diagnosed ALL, with good response rates. This review discusses novel immunotherapeutic options, including bispecific antibodies, ADCs, and CAR T-cell–based therapies, in the upfront setting. It also discusses the incorporation of novel agents either as monotherapy or in combination with cytotoxic chemotherapy and describes our views on how best to use these agents in patients with newly diagnosed disease.

Keywords
Acute lymphoblastic leukemia (ALL), blinatumomab, chimeric antigen receptor (CAR) T-cell therapy, inotuzumab ozogamicin

Introduction

Treatment for acute lymphoblastic leukemia (ALL) in children and adults continues to evolve, with significant advances made over the last 2 decades. Several modalities have been developed that notably emphasize use of the harnessing the power of the immune system to eradicate malignant cells. In the last 20 years, 5-year overall survival (OS) in ALL has steadily improved across all ages. The largest gains in survival have been in children aged 1 to 14 years, in whom the 5-year OS rate is now greater than 93% following upfront intensive multiagent chemotherapy. In contrast, however, the 5-year OS rates with intensive chemotherapy are only 59% in patients aged 20 to 39 years, 29% in those aged 60 to 69 years, and 13% in those aged 70 years and older.[1] Despite high initial complete response (CR) rates, more than half of adults with a diagnosis of ALL ultimately experience

relapse and outcomes have historically been poor in both children and adults, with a 5-year OS rate of less than 50% in children and a dismal rate of less than 10% in adults.[2-5] Immunotherapy has profoundly affected the landscape of relapsed ALL, particularly B-cell ALL (B-ALL), in which agents like the CD3-CD19 bispecific antibody blinatumomab (Blincyto, Amgen) and the CD22 antibody-drug conjugate (ADC) inotuzumab ozogamicin (InO; Besponsa, Pfizer), as well as chimeric antigen receptor (CAR) T-cell therapy, have shown impressive results. Rituximab, a monoclonal antibody directed toward CD20, was the first immunotherapy against B-ALL. Although most of the initial trials with immunotherapy focused on relapsed or refractory (R/R) B-ALL, immunotherapeutic agents are now being successfully integrated into frontline therapy with excellent outcomes. This review discusses the use of immunotherapy in newly diagnosed ALL and how best to use it in clinical practice.

Upfront Immunotherapy for Philadelphia Chromosome–Negative B-Cell ALL

CD20-Targeted Antibodies: Rituximab and Obinutuzumab

Rituximab is a chimeric (murine-human) monoclonal antibody targeting the CD20 antigen found on the surface of normal and malignant B cells.[6] Approximately 40% to 50% of cases of B-ALL are CD20-positive, defined as a CD20-positive blast count of at least 20%.[7-9] CD20 expression in adult B-ALL is a negative prognostic factor, associated with a higher incidence of relapse (65% vs 42%; *P*<.001) and a lower 3-year OS rate (27% vs 40%; *P*=.03).[10,11]

Clinical Trials With Rituximab. Initial trials added rituximab to the standard induction chemotherapy backbone for newly diagnosed CD20-positive B-ALL. In the MD Anderson Cancer Center (MDACC) trial, 282 adults and adolescents with de novo Philadelphia chromosome–negative (Ph-negative) B-ALL were treated with the hyper-CVAD chemotherapy regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) with or without rituximab. Patients received 2 doses of rituximab during each of the first 4 cycles. The addition of rituximab improved the 3-year CR rate (70% vs 38%; *P*<.001) and the 3-year OS rate (75% vs 47%; *P*=.003) in patients younger than 60 years. However, older patients derived no additional benefit from rituximab and no additional toxicity.[12,13] The German Multicenter Study Group for Adult ALL (GMALL) investigated rituximab in patients with standard-risk B-ALL. Although the rates of CR, early death, and failure were similar in the groups with and without rituximab (94% vs 93%, 5% vs 4%, and 1% vs 2%, respectively), molecular CR (measurable residual disease [MRD] $<10^{-4}$) was achieved faster in the rituximab recipients, with higher rates of MRD negativity at day 21 (60% vs 19%) and week 16 (89% vs 57%).[14] This observation was confirmed by the large multicenter randomized GRAALL-2005 study from the Group for Research on Adult Acute Lymphoblastic Leukemia. A total of 209 adults aged 18 to 59 years were randomly assigned to a pediatric-inspired regimen with or without rituximab. At a median follow-up of 30 months, the addition of rituximab was associated with a lower 4-year cumulative incidence of relapse (25% vs 41%) and a higher event-free survival (EFS) rate (55% vs 43%; hazard ratio [HR], 0.52). CR rates were similar (92% vs 90%), and the rates of nonrelapse mortality (NRM) at 2 years were comparable (12% vs 12%). The OS rates were not statistically different in the entire cohort (61% vs 50% at 4 years; HR, 0.70), but for patients who underwent allogeneic hematopoietic cell transplant (allo-HCT) in first CR, OS was better in the rituximab arm (HR, 0.55; 95% CI, 0.34-0.91).[15] In the UK NCRI phase 3 randomized trial from the National Cancer Research Institute, patients aged 25 to 65 years did not show a significant improvement in EFS when 4 doses of rituximab were added to standard-of-care chemotherapy, regardless of level of CD20 expression. The 3-year EFS rates were 43.7% vs 51.4% (HR, 0.85), with relapse rates lower in the rituximab group (26.3% vs 31.1%; HR, 0.85), but these results were not statistically significant (*P*=.29).[16] For the full benefit of rituximab in B-ALL, the administration of more doses throughout the entire course of therapy is likely required.

Ofatumumab (Arzerra, Novartis), another fully humanized anti-CD20 monoclonal immunoglobulin G1 antibody, was tested in an MDACC phase 2 trial.[17-19] In this trial, the outcome of patients with newly diagnosed Ph-negative B-ALL who received hyper-CVAD with ofatumumab was superior to the outcome of those treated with hyper-CVAD +/- rituximab (4-year EFS rates, 61% vs 43%; 4-year OS rates, 66% vs 48%).[20]

From the above studies, it is clear that rituximab, when added to chemotherapy, improves outcomes in younger patients (<60 years of age) with CD20-positive B-ALL. Its benefit in older patients or those with CD20 expression below 20% is less clear and warrants further research. The addition of rituximab with the pediatric-inspired regimens is supported, but the optimal dosing and timing remain areas of further investigation. We believe that the addition of rituximab to upfront chemotherapy in CD20-positive B-ALL is associated with better outcomes in younger patients.

CD19-Targeted Antibodies: Blinatumomab

CD19 is a type I transmembrane glycoprotein that is expressed in both normal B cells and leukemic blasts, and it plays an essential role in B-cell differentiation.[21,22]

Blinatumomab is a bispecific antibody that targets CD19 on B cells and CD3 on cytotoxic T cells, directing T cells to attack B-cell leukemic blasts.[21] It first received US Food and Drug Administration (FDA) approval in 2014 for R/R Ph-negative B-ALL in adults,[23] with approval expanded in 2017 to include Ph-positive B-ALL and in 2018 to cover both children and adults with MRD of 0.1% or greater in first or second CR.[24,25] Full FDA approval was based on results from the TOWER and ALCANTARA trials. In the phase 3 TOWER trial, outcomes with blinatumomab were superior to those with chemotherapy, with CR rates of 34% vs 16% and CR rates with incomplete hematologic recovery (CRi) of 44% vs 25% (P<.001). OS (7.7 vs 4 months) and median CR duration (7.3 vs 4.6 months) were significantly better in the blinatumomab group.[21] In a follow-up study to the ALCANTARA trial of patients with R/R Ph-positive B-ALL, a propensity score analysis showed better CR/CRi rates (36% vs 25%) and an OS HR of 0.77 (95% CI, 0.61-0.96) in the patients who received blinatumomab than in historical controls, indicating a 23% reduction in risk of death.[26] In the BLAST trial of MRD-positive ALL, 88 of 113 evaluable patients (78%) achieved MRD negativity after 1 cycle of blinatumomab, with median relapse-free survival (RFS) of 23.5 vs 5.6 months (P=.002) and OS of 38.8 vs 12.4 months (P=.002) in the MRD-negative vs MRD-positive patients, respectively.[27] However, blinatumomab was less effective in the patients with a high disease burden,[28,29] extramedullary disease,[30] programmed death ligand 1 (PD-L1) expression on blasts,[31] or loss/alteration of CD19 expression.[32] Because of its short half-life, continuous infusion over 28 days is required, and the drug carries a potential risk for cytokine release syndrome (CRS) during the first cycle, necessitating inpatient administration. Ongoing studies are comparing the economic effect of blinatumomab with that of other salvage options.[33] In a recently published phase 1b trial, 29 patients were treated with subcutaneous blinatumomab in either of 2 dosing schedules: 250 μg once daily for week 1 and 500 μg 3 times per week thereafter (250 μg/500 μg) or 500 μg once daily for 1 week and 1000 μg 3 times per week thereafter (500 μg/1000 μg). The results were promising, with high response rates and acceptable toxicity in patients with heavily pretreated R/R B-ALL, improving convenience and potentially reducing costs.[34] Treatment-related grade 3 CRS events at dose levels of 250 μg/500 μg and 500 μg/1000 μg were 21.4% and 23.1%, respectively. The rates of grade 3 neurologic events, including immune effector cell–associated neurotoxicity (ICANS), were 42.9% and 23.1%, respectively. The reason for the higher rate of neurologic events at the lower dose level is unclear. A larger sample size of patients may be needed for further evaluation.[34]

Upfront Blinatumomab With Chemotherapy in Younger Patients. The exciting results of blinatumomab in the R/R and MRD-positive settings led to its integration with chemotherapy in upfront treatment. Several phase 2 studies have demonstrated that blinatumomab and InO, either alone or in combination with chemotherapy, are effective. The phase 2 GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) LAL2317 trial administered 2 courses of blinatumomab after standard pediatric-inspired induction chemotherapy. The first dose was administered after early consolidation ("cycle 3") and the second after late consolidation ("cycle 6"). A total of 149 patients were enrolled in this study (median age, 41 years; range, 18-65 years; 18% >55 years); 132 entered remission, 122 received blinatumomab, and 109 had an MRD assessment before and after the first dose of blinatumomab. The percentage of patients with MRD negativity increased from 72% to 93% (P<.001) after blinatumomab, with 23 of 30 MRD-positive patients (76%) becoming MRD-negative. At a median follow-up of 38.1 months, median OS and disease-free survival (DFS) were not reached and the estimated 3-year OS and DFS rates were 71% and 65%, respectively, with an excellent outlook for patients aged 18 to 40 years with early MRD negativity (DFS rate, 92%). Pre-blinatumomab MRD positivity predicted a worse outcome, especially in patients with high-risk genetic features (*KMT2A* rearrangements, *IKZF1* deletion with or without additional copy number alterations, and other adverse molecular rearrangements and aberrations involving *CLRF2*, *JAK2*, *ABL1*, *TP53*, and *HLF:TCF3*) and in those with a high white blood cell count. Notably, the 3-year survival rate of blinatumomab-treated patients was 82%. The results were remarkable in the patients assigned to chemotherapy (3-year OS, 91%; 3-year DFS, 75%) and somewhat less favorable in those assigned to allo-HCT (3-year OS, 59%; 3-year DFS 50%) owing to their higher risk of relapse and transplant-related mortality, although with a better outcome in transplant recipients (OS, 69%; DFS, 63%). The global risk of relapse and incidence of remission mortality were 28% and 7%, respectively. This chemotherapy-blinatumomab trial yielded remarkable results that require further improvement in high-risk patients and those with early MRD persistence.[35]

The phase 2 MDACC trial evaluated sequential blinatumomab added to hyper-CVAD in younger adults with newly diagnosed Ph-negative B-ALL. A total of 38 patients (median age, 37 years; range, 29-46) were treated. After a median follow-up of 37 months, 79% of the patients were alive at the last follow-up, and 74% were in continuous first response. The 3-year RFS rate was 73%, with a 3-year RFS rate of 77% in patients aged 18 to 39 years and of 68% in those aged 40 years and

older, with no relapses beyond 2 years. The 3-year RFS rate was 84% for patients achieving MRD negativity after 1 cycle of blinatumomab vs 50% for those who did not achieve MRD negativity. Multiparameter flow cytometry was used to assess MRD, with a sensitivity of 1×10^{-4} on each bone marrow aspirate. MRD was also assessed by next-generation sequencing (the clonoSEQ MRD assay), with a sensitivity of 1×10^{-6}. The 3-year RFS rate was 82% (55%-94%) for patients without high-risk disease features before treatment and 66% (41%-82%) for those with at least one high-risk feature. High-risk disease was defined as follows: persistent MRD positivity after 2 cycles of intensive chemotherapy, high-risk cytogenetics (eg, *KMT2A* rearrangement, complex karyotype, low hypodiploidy or near-triploidy), *CRLF2* overexpression by flow cytometry (suggestive of Ph-like ALL), or presence of a *TP53* mutation. No treatment-related deaths occurred, although infections were common (37% during induction and 71% during consolidation). CRS of any grade occurred in 15% of patients, with grade 3 or higher CRS developing in only 1 patient. Blinatumomab-related neurologic events of any grade occurred in 47% of patients, with grade 3 ICANS developing in 11% (4 patients: 2 encephalopathy, 1 ataxia, and 1 delirium). No deaths due to these events were reported. Allo-HCT was reserved for patients with at least one high-risk genomic feature; 15 of the 17 patients without high-risk features did not undergo allo-HCT and only one relapsed, suggesting that blinatumomab-containing regimens may be effective without allo-HCT for some patients. In contrast, more than half of the patients with high-risk features underwent allo-HCT in first response, and these patients had a 3-year OS rate of 76%. The 10 patients with genomic features historically classed as high-risk did not receive allo-HCT, and 6 of these patients remained in continuous response at the last follow-up, indicating potential cure with blinatumomab-based regimens in some patients with high-risk features.[36] Although these results appear encouraging, it is worth noting that the study was a single-arm phase 2 trial and the median follow-up is 37 months, so a longer follow-up is needed to determine benefit.

In the French phase 2 GRALL-2014-QUEST trial, high-risk patients with a median age of 35 years (range, 18-60) and a *KMT2A* rearrangement (*KMT2A*-r), *IKZF1* intragenic deletion (*IKZF1*del), and/or MRD of at least 10^{-4} after induction received up to 5 cycles of blinatumomab during the consolidation and maintenance phases, or as a bridge to allo-HCT. Among the 94 evaluable patients, the 2.5-year OS rate was 79% and the DFS rate was 72%. Patients with very high-risk disease (MRD ≥0.1% after induction cycle 1 and/or ≥0.01% after induction cycle 2) had worse DFS rates (68.8% vs 90.6% for others). Factors significantly associated with better DFS included *DUX4*/*ERG* deletion, low MRD before blinatumomab, and complete MRD response after blinatumomab.[37] This trial underscored the role of blinatumomab in improving outcomes for high-risk patients and reducing the need for allo-HCT.

The Australasian Leukaemia and Lymphoma group (ALLG) introduced early blinatumomab to reduce the burden and intensity of chemotherapy. They observed a CR rate of 100%, with 70% of patients achieving an MRD response after the first cycle (1B), which increased to 83% after the second cycle (2B) of blinatumomab. The estimated 2-year EFS and OS rates were 62% and 69%, respectively.[38] In a recently published study in children with newly diagnosed standard-risk B-ALL, blinatumomab in combination with chemotherapy achieved an estimated 3-year DFS rate of 96.0%±1.2% with blinatumomab and chemotherapy vs 87.9%±2.1% with chemotherapy alone at a median follow-up of 2.5 years. The estimated 3-year DFS rate among patients with an average risk of relapse was 97.5%±1.3% with blinatumomab and chemotherapy vs 90.2%± 2.3% with chemotherapy alone. Among those with a higher risk of relapse, the corresponding values were 94.1%±2.5% and 84.8±3.8%, respectively, suggesting that the addition of blinatumomab to combination chemotherapy in patients with newly diagnosed childhood standard-risk B-ALL with average or higher risk of relapse significantly improved DFS.[39]

The phase 3 Eastern Cooperative Oncology Group and American College of Radiology Imaging Network (ECOG-ACRIN)-E1910 international multicenter trial randomized 224 of 488 adult patients with newly diagnosed Ph-negative B-ALL (aged 30-70 years) who achieved an MRD-negative CR after induction/intensification to receive conventional chemotherapy with or without blinatumomab. Patients received multiagent induction therapy with a Berlin-Frankfurt-Münster–like regimen adapted from E2993/UKALLXII.[40,41] Pegaspargase (Oncaspar, Shire) was added for patients younger than 55 years, and rituximab was added for patients with CD20-positive B cells. After induction of remission, patients who achieved CR/CRi proceeded to intensification with high-dose methotrexate plus pegaspargase, after which remission and MRD were determined with 6-color flow cytometry (MRD negativity was defined as $<1\times10^{-4}$). MRD-negative patients were randomized to 4 cycles of consolidation chemotherapy alternating with 4 cycles of blinatumomab or to chemotherapy alone. After the FDA approval of blinatumomab for patients with MRD positivity, those with MRD positivity were assigned to the blinatumomab arm. All patients received maintenance therapy with 6-mercaptopurine/vincristine/methotrexate/prednisone (POMP). For the entire cohort, the CR/CRi rate after induction was 81%. The addition of blinatumomab significantly

improved outcomes in MRD-negative patients. The 3-year OS rates were 85% in the blinatumomab group vs 68% in the chemotherapy-alone group (*P*=.002), and the 3-year RFS rates were 80% vs 64%, respectively (HR, 0.53; 95% CI, 0.32-0.87). The incidence of grade 3 or higher neuropsychiatric events was higher in the blinatumomab group than in the control group (23% vs 5%).[42] Unlike sequential blinatumomab duration and cycles of hyper-CVAD, which were reduced, consolidation chemotherapy duration in the E1910 protocol was not reduced and yet the regimen was safe and significantly more effective than chemotherapy alone. Among 132 patients younger than 55 years, the 3-year OS rates with blinatumomab vs chemotherapy alone were 95% vs 79% (HR, 0.16; 95% CI, 0.05-0.47), and the 3-year RFS rates were 87% vs 70% (HR, 0.31; 95% CI, 0.14-0.69). Among 93 patients aged 55 years and older, the 3-year OS rates were 70% vs 65% (HR, 0.66; 95% CI, 0.33-1.35), and the 3-year RFS rates were 69% vs 57% (HR, 0.74; 95% CI, 0.39-1.43). Although the benefit was more pronounced in younger patents, it was still evident in patients aged 55 years and older.[42] The smaller benefit in older patients may be explained by their not receiving pegaspargase, higher-risk features of disease, or their not receiving allo-HCT owing to age and comorbidities.[43] Subgroup analysis revealed that blinatumomab was particularly beneficial for patients with undetectable MRD (HR, 0.51; 95% CI, 0.27-0.97; *P*=.038), whereas patients with MRD between undetectable and 0.01% had no significant OS difference (median OS, not reached vs 38.0 months; HR, 0.35; 95% CI, 0.06-1.94; *P*=.16).[43] This is the first randomized multicenter study showing the benefit of upfront sequential blinatumomab with chemotherapy in Ph-negative B-ALL. In this trial, morphologic CR with or without complete count recovery after induction was observed in 395 patients (81%), but only 286 of these patients reached the randomization or assignment step after the intensification phase. The remainder of the patients did not do so for reasons that included relapse, toxic effects, death, withdrawal of consent, and transplant. The results supported the FDA approval of blinatumomab for a third indication, as part of consolidation treatment for patients of all ages.

These studies collectively highlight the potential of combining blinatumomab with intensive chemotherapy in the upfront treatment of newly diagnosed Ph-negative B-ALL, particularly in adults younger than 55 years. The combination has improved CR and MRD negativity rates and has reduced relapse rates, suggesting that it may become a new standard of care in Ph-negative adult B-ALL. For patients younger than 55 years, we recommend incorporating blinatumomab with intensive chemotherapy.

Blinatumomab in Elderly Patients. Blinatumomab has been studied as a treatment for older patients with B-ALL; these patients typically have poor outcomes with chemotherapy, with 5-year OS rates of 10% to 20%.[44] In the SWOG 1318 study, single-agent blinatumomab was used for 1 to 2 cycles as induction until response, followed by 3 cycles of consolidation and 18 months of POMP maintenance therapy. In 29 patients aged 65 years and older, the CR rate was 66% and the 3-year DFS and OS rates were both 37%, which compared favorably with the rates in historical controls for this age group.[45] A GMALL study evaluated sequential blinatumomab with chemotherapy in patients aged 56 to 76 years. Those with a CR or partial response (PR) after chemotherapy received blinatumomab, whereas those with induction failure received a second induction cycle of chemotherapy, followed by 3 consolidation cycles of blinatumomab and up to 2 years of standard maintenance. Of 33 evaluable patients, 85% responded, 9% failed treatment, and 29% achieved a molecular response. One-third of those with induction failure after the first cycle achieved a CR after the second, resulting in a CR rate of 83%, and 82% of the patients with a CR had a molecular response after blinatumomab. The OS rates at 1 year were 100% for patients aged 55 to 65 years and 66% for those older than 65 years. The 1-year DFS rate was 89%, with no deaths occurring during blinatumomab treatment.[46]

The phase 3 Golden Gate study is currently enrolling patients with newly diagnosed Ph-negative B-ALL aged 55 years and older or 40 to 54 years with severe comorbidities. The study is randomizing patients to receive either blinatumomab alternating with low-intensity chemotherapy or standard chemotherapy. Patients randomized to the investigational arm receive blinatumomab for 2 cycles during induction, 2 cycles during consolidation, and 3 cycles during maintenance therapy, alternating with chemotherapy. In a preliminary safety run-in phase, among 10 patients in the investigational arm, no deaths occurred, the treatment was well tolerated, and all patients achieved a CR. Additionally, 90% of the patients had an MRD response of less than 10^{-4} after the first induction cycle.[47]

In summary, the incorporation of blinatumomab in frontline regimens for older patients appears promising, with favorable tolerability and efficacy, low rates of treatment-related mortality, high rates of MRD negativity, and favorable short-term survival outcomes according to early reported data. Studies are ongoing to determine the best use of blinatumomab. We therefore recommend enrolling older patients (>55 years) with newly diagnosed Ph-negative B-ALL in frontline immunotherapy trials that would minimize chemotherapy-related toxicities and potentially improve outcomes.

CD22-Targeted Agents: Inotuzumab Ozogamicin

InO is a CD22-directed humanized monoclonal antibody

linked to the cytotoxin N-acetyl-γ-calicheamicin via a butanoic acid linker. CD22 is a type I transmembrane protein that inhibits B-cell receptor signaling.[48-52] The phase 3 INNOVATE study compared InO with standard intensive chemotherapy in R/R B-ALL and showed significant benefits with InO, leading to FDA approval.[53] The trial showed significantly higher rates of CR (80.7% vs 29.4%; *P*<.001) and MRD negativity (78.4% vs 28.1%; *P*<.001) with InO. The median duration of remission was longer for InO (4.6 vs 3.1 months; *P*=.03), and more patients proceeded to allo-HCT (41% vs 11%; *P*<.001). Survival analysis showed longer PFS with InO (5.0 vs 1.8 months; *P*<.001) and OS (7.7 vs 6.7 months; *P*=.04). The most significant nonhematologic toxicity was vaso-occlusive disease (VOD) of any grade (11% vs 1%).[53]

Upfront InO With Combination Chemotherapy in Older Adults. Given the success of InO in the R/R setting, several studies examined its use in the frontline setting. The MDACC conducted a single-center phase 2 study combining InO with cyclophosphamide, vincristine, and dacarbazine as a lower-intensity induction regimen (mini-hyper-CVD) in newly diagnosed Ph-negative B-ALL. Of 52 patients enrolled, 48 received InO starting on day 3 of the first 4 cycles at doses between 1.3 and 1.8 mg/m^2, followed by 1.0 to 1.3 mg/m^2 in subsequent cycles. The rates of CR/CRi and CR with incomplete platelet recovery (CRp) were 98% (85% CR, 10% CRp, and 2% CRi), with 96% responders achieving MRD negativity (assessed by multiparameter flow cytometry [MFC], sensitivity <10^{-4}). After a median follow-up of 29 months, the 3-year PFS rate was 49% and the OS rate was 56%.[54] Updated results showed a 5-year CR rate of 76% and an OS rate of 46%.[55] However, 22 patients (42%) could not complete induction or consolidation owing to therapy-related complications, and 6 patients (12%) died of treatment-related complications, including 5 with infections and 1 with VOD. All patients had hepatic adverse events, with 17 of these (33%) grade 3 or higher. VOD developed in 4 patients (8%) after a median of 3 cycles (range, 1-4), including 1 patient after allo-HCT. Despite the reduced intensity of this regimen, a substantial proportion of patients older than 70 years died in remission, raising concerns for potential late toxicity. The GMALL-Initial-1 study combined InO at 1.8 mg/m^2 in cycle 1 of induction with dexamethasone, followed by 1.5 mg/m^2 in cycles 2 and 3. Patients in CR proceeded with conventional consolidation, reinduction, and maintenance therapy. Among the 43 patients treated, the CR/CRi rate was 100%, with MRD negativity rates of 53% after cycle 2 and 74% after cycle 3. The 3-year EFS and OS rates were 55% and 73%, respectively. Nonfatal VOD occurred in 1 patient.[56] The French EWALL-INO phase 2 study evaluated InO with low-intensity chemotherapy in older patients. It included a 2-part induction regimen following a 5-day corticosteroid pre-phase. In induction 1, InO at 1.8 mg/m^2 was given with weekly vincristine and pulse dexamethasone. In induction 2, patients in CR/CRp received InO at 1.0 mg/m^2 with a week of dexamethasone and low-dose cyclophosphamide, plus triple intrathecal chemotherapy. For patients in CR/CRp, this was followed by 6 cycles of consolidation followed by POMP maintenance for up to 18 months. Among 131 treated patients, the CR/CRp rate was 90% (85% CR, 5% CRp), and 81% achieved MRD negativity after 2 courses of induction. The 2-year OS rate was 54%, and the 2-year leukemia-free survival rate was 50%. Of the 118 patients in CR/CRp, 11 (9%) received an allo-HCT, and VOD developed in 3 patients (2%), including 1 patient after allo-HCT.[57]

The single-arm, phase 2 Alliance A041703 study investigated a completely chemotherapy-free induction regimen for elderly patients with newly diagnosed Ph-negative B-ALL. In this study, InO was given for induction course 1A at 1.8 mg/m^2 fractionated, repeated in cycle 1B if in CR/CRi or induction course 1C if not, and followed by blinatumomab consolidation. The CR/CRi rate among 33 treated patients was 85% and reached 97% after consolidation. After a median follow-up of 22 months, the 1-year EFS rate was 75% and the 1-year OS rate was 84%. The 12 events that occurred included 9 relapses, 2 deaths in remission, and 1 death without remission that was due to VOD.[58] The data support further study of this highly active and tolerable chemotherapy-free regimen, which demonstrates durable remissions and requires longer follow-up to evaluate its efficacy and safety fully.

Upfront InO in Younger Adults With Combination Chemotherapy. Combination approaches using InO are being explored in younger adults with newly diagnosed Ph-negative B-ALL. The phase 2 MDACC study evaluated the combination of hyper-CVAD plus blinatumomab with or without InO in patients aged 60 years or younger. The regimen included conventional hyper-CVAD alternating with high-dose methotrexate and cytarabine for up to 4 cycles, followed by 4 cycles of blinatumomab consolidation and then POMP and blinatumomab maintenance. In the first cohort, all 38 patients responded, with 97% achieving MRD negativity by flow cytometry. The 3-year RFS and OS rates were 73% and 81%, respectively.[36] After the first 38 patients, the study was modified to add InO (0.3 mg/m^2) on days 1 and 8 of 2 cycles of methotrexate/cytarabine in the hyper-CVAD regimen and to 2 of the 4 cycles of blinatumomab consolidation. As of June 2023, 75 patients were treated, with 37 receiving InO and the remaining 38 not receiving InO. In the 59 patients with active disease at study initiation, the CR rate was 100%, and 92% achieved MRD negativity. After a median follow-up of 26 months, the 3-year OS rate was 88% and the 3-year

RFS rate was 79%. The 18-month RFS rate was 92% in the patients treated with InO vs 76% in those who did not receive InO (*P*=.18), and the 18-month OS rates were 100% vs 84% (*P*=.04). Among 23 patients (31%) with high-risk ALL (complex karyotype with ≥5 abnormalities, 11q23 translocations) who proceeded to allo-HCT in first CR, no cases of VOD occurred.[59,60]

The multicenter phase 3 Alliance A041501 study of patients aged 18 to 39 years with newly diagnosed ALL evaluated adding 2 cycles of InO (1.5 mg/m^2/cycle) to an intensive pediatric-inspired CALGB 10403 chemotherapy regimen. Patients achieving CR/CRi or PR were randomized 1:1 to receive InO or continue the CALGB 10403 backbone. Following induction in the experimental arm, 2 cycles of InO (1.5 mg/m^2/cycle) were administered. A total of 273 patients were enrolled, with an overall CR rate of 86.8%; 46 patients were not randomized owing to death (5), withdrawal (6), ineligibility (3), toxicity (5), receipt of nonprotocol therapy (8), progression (8), or other (14). At a median follow-up of 28.3 months for randomized patients, the 3-year EFS rate was 69.0% for the InO arm and 66.7% for the control arm (HR, 0.97; 0.58-1.63). The 3-year OS rate was 79.4% (71.0%-88.7%) for the InO arm and 80.3% (71.9%-89.6%) for the control (HR, 1.05; 0.55-2.01). The rate of undetectable MRD at course 2, day 56, was 80.6% in the InO arm and 74.2% in the control arm. Univariate analysis showed improved EFS with InO in patients with a positive low-density microarray card (which tests for Ph-like ALL) and Hispanic ethnicity. There were 22 grade 5 events, 7 of which occurred before randomization. Of the 15 grade 5 events in the randomized cohort, 12 were reported in the InO arm and 3 in the control arm. Of the 12 grade 5 events in the InO arm, all occurred during courses of intensive consolidation complicated by prolonged pancytopenia infection/sepsis (8), hepatobiliary events in the setting of infection (2), multiorgan failure (1), or postsurgical complications (1). These events occurred after InO during course 2 (3), course 3 (5), or course 4 (4). The primary endpoint of this trial was to determine if the addition of InO improved EFS with the pediatric-inspired regimen CALGB 10403 without censoring for allo-HCT. Although this endpoint was not met, the data provide compelling evidence for the continued use of pediatric regimens in young adults with Ph-negative B-ALL, and InO may still be efficacious if late toxicity can be mitigated.[61] Similar observations were made in the second safety analysis of the Children's Oncology Group (COG) AALL1732 phase 3 study, in which high infection rates in the chemotherapy-plus-InO arm led to a 20% reduction in InO dosing.[62,63] The ALL-Together1 frontline trial (NCT04307576) is evaluating the addition of 6 weekly doses of InO at 0.5 mg/m^2 per dose after intensive chemotherapy in children with intermediate- to high-risk ALL. These ongoing trials will be critical in determining optimal dosing strategies that balance toxicity risk with improved outcomes.

These studies suggest that InO is highly effective and well tolerated as frontline therapy for Ph-negative B-ALL and appears independent of disease burden. However, in combination with chemotherapy, it may lead to significant toxicity. Fractionated dosing with chemotherapy or blinatumomab may improve safety without compromising efficacy. Further studies are needed to optimize dosing strategies and evaluate the contributions of InO and blinatumomab in treatment outcomes.

Upfront Immunotherapy for Ph-Positive and Ph-Like B-Cell ALL

The t(9;22) translocation is the most common cytogenetic abnormality in adult ALL, accounting for 20% to 25% of cases.[64,65] Historically, the treatment of Ph-positive B-ALL consisted of intensive induction chemotherapy followed by allo-HCT. However, the long-term outcomes with this approach were suboptimal, with 5-year survival rates ranging from 10% to 30% and increasing to 35% to 45% with allo-HCT.[66-68] With the use of tyrosine kinase inhibitors (TKIs) in the frontline setting, CR rates have improved to 90% to 100%, and the 5-year OS rate is approximately 50% with or without allo-HCT.[69-73] A recent study using the third-generation TKI ponatinib (Iclusig, Takeda) in the frontline setting with chemotherapy has shown an impressive 3-year OS rate of 83%.[72]

Frontline Blinatumomab for Ph-Positive ALL

Patients with Ph-positive B-ALL who experience relapse after TKI therapy have poor outcomes, necessitating novel approaches.

The GIMEMA LAL2116 (D-ALBA) trial evaluated a chemotherapy-free combination induction regimen of dasatinib and corticosteroids for 3 months, followed by 2 to 5 cycles of blinatumomab, in patients with newly diagnosed Ph-positive B-ALL. This approach achieved a CR rate of 98% in 63 adults with newly diagnosed Ph-positive B-ALL. The molecular response rate improved from 29% to 60% after the first cycle of blinatumomab, with further increases after additional cycles.[74] The 4-year DFS rate was 76%, OS was 81%, and EFS was 75%. The *IKZF1*^{plus} genotype was associated with a worse prognosis (4-year DFS rate of 46%). A recent update reported 9 relapses, including 4 hematologic relapses, 4 cases of isolated central nervous system (CNS) disease, and 1 nodal relapse, and a T315I mutation was detected in 6 of the 8 patients with relapse.[75] In the SWOG 1318 study, which combined dasatinib and blinatumomab in patients aged 65 years and older with Ph-positive B-ALL, the CR rate was 92%, and 31% achieved complete molecular remission (CMR).

Median OS was 6.5 years and median DFS was not reached as of June 29, 2023. The 3-year DFS and OS rates were 72% and 75%, respectively.[76,77] In the MDACC trial combining ponatinib (a TKI effective against *ABL1* mutations like T315I) with blinatumomab, the CMR rate was 83%, with a 3-year EFS rate of 77% and OS rate of 91% in 60 patients. Unlike in the D-ALBA and SWOG trials, blinatumomab was introduced with ponatinib on day 1, likely contributing to high CMR rates. Only 2 patients underwent allo-HCT in first remission, suggesting that this chemotherapy-free regimen may obviate the need for allo-HCT in some patients.[78] These outcomes suggest that combining TKI and blinatumomab can be effective in older adults, who typically cannot tolerate intensive therapies. However, CNS relapse remains a significant concern in patients with Ph-positive B-ALL treated with chemotherapy-free regimens. Both the D-ALBA and SWOG trials reported isolated CNS relapses (4 patients in D-ALBA and 2 in the SWOG trial).[75,77,79] To address this problem, the MDACC trial increased the number of prophylactic intrathecal chemotherapy doses from 12 to 15, and the ongoing GIMEMA LAL2820 trial (NCT04722848) is doing the same.[79]

The ECOG-ACRIN Cancer Research Group is leading a US intergroup randomized phase 3 study (EA9181, NCT04530565) comparing blinatumomab plus a TKI (dasatinib or ponatinib) with hyper-CVAD chemotherapy plus a TKI in patients with newly diagnosed Ph-positive B-ALL. Similarly, the GIMEMA study is comparing chemotherapy with imatinib vs blinatumomab with ponatinib induction (ALL2820, NCT04722848). These studies will likely transform the paradigm of frontline therapy for Ph-positive B-ALL.

Frontline Inotuzumab for Ph-Positive B-Cell ALL and Ph-Like ALL

InO has not been evaluated in the frontline setting for Ph-positive or Ph-like B-ALL. It has shown efficacy in the R/R setting without a TKI in the INO-VATE trial and in a single-center study in combination with bosutinib (Bosulif, Pfizer).[80,81] A phase 2 study using InO with dasatinib and dexamethasone for upfront treatment is ongoing (NCT04747912).

Upfront CAR T-Cell Therapy

No frontline studies of CAR T-cell therapy for newly diagnosed B-ALL have been conducted. In the United States, 3 autologous CAR T-cell products are currently approved for R/R B-ALL: tisagenlecleucel (tisa-cel; Kymriah, Novartis) for children and young adults up to age 25 years, brexucabtagene autoleucel (brexu-cel; Tecartus, Kite) for adults, and obecabtagene autoleucel (Aucatzyl, Autolus) for adults, on the basis of the phase 2 ELIANA, ZUMA-3, and FELIX trials, respectively.[82-89]

Although most older adults with newly diagnosed B-ALL may attain CR following low-intensity chemotherapy with or without InO or blinatumomab, consolidation after remission poses significant challenges.

Older patients treated with consolidation therapies such as chemotherapy and allo-HCT frequently experience long-term treatment-related complications or treatment failure. As a result, the earlier use of CAR T-cell therapy in the treatment of Ph-negative B-ALL is imperative. CAR T-cell therapy has been effective in patients with a low tumor burden or MRD positivity.[90-93] In a recently reported study from China, CD19 CAR T-cell therapy was used in the frontline setting for patients with newly diagnosed Ph-positive B-ALL who had achieved morphologic remission after initial induction with systemic and intrathecal chemotherapy and TKI therapy. Following CR, patients received 1 cycle of an investigational CD19 CAR T-cell product, followed by 3 additional cycles of CD19 CAR T-cell therapy in combination with CD19-positive feeding T cells and TKI therapy. A total of 13 patients were treated in the phase 1 portion of the study. A total of 62% of patients were in CMR before CAR T-cell therapy and 92% were in CMR after all CAR T-cell therapy cycles. At the time of reporting, only one patient had experienced CNS relapse. Grade 1 CRS was observed in 69% of patients, primarily following the first CAR T-cell infusion, and no cases of ICANS occurred.[94] A similar approach was retrospectively reported recently, in which CD19 CAR T-cell therapy was used to treat 2 children with high-risk B-ALL who were ineligible for allo-HCT. Both children maintained long-term MRD-negative remission following CD19 CAR T-cell therapy, although both received subsequent therapies, including CD22 CAR T-cell therapy in one case.[95] Currently, an ongoing pediatric consortium study is using tisagenlecleucel in MRD-positive CR1 at the end of consolidation (NCT03876769). In addition, an upcoming multi-institutional study will investigate brexucabtagene autoleucel in adults with persistent MRD following induction therapy.

Several other ongoing studies are evaluating CAR T-cell therapy for MRD-positive B-ALL after induction chemotherapy (NCT05535855, NCT04788472, NCT04740203, NCT03919526, NCT06078306, and NCT06481241). A phase 1/2 study using bispecific CAR T-cell therapy targeting CD19 or CD19/CD22 demonstrated effectiveness in eradicating MRD without significant toxicities.[96,97]

Upfront Immunotherapy in T-Cell ALL

T-cell ALL (T-ALL) originates from early T-cell progenitors and comprises 25% of adult and 15% of pediatric ALL cases.[98] Treatment for newly diagnosed T-ALL typically involves multiagent chemotherapy, but immunotherapy is

in the early stages of development. Targeting cell surface receptors is a promising strategy, but because immune cells, including normal T cells, may express the same receptors, serious adverse effects like fratricide of normal T cells with T-cell depletion can occur. Alemtuzumab, an anti-CD52 humanized monoclonal antibody, was trialed in a study of patients with R/R T-ALL. This study also included a few patients who had not received prior therapies, but none of them achieved a response, and significant toxicities occurred, including viral reactivations.[99,100]

The CD38-targeting monoclonal antibody daratumumab (Darzalex, Janssen Biotech) is effective in children and young adults when combined with chemotherapy in R/R disease, as shown in the DELPHINUS study.[101] Studies are evaluating its use in newly diagnosed very high-risk T-ALL (NCT06253637, DARATALL-VHR) and in R/R disease (NCT05289687, NCT03384654, NCT03207542, NCT06570915). Ongoing trials are also investigating monoclonal antibodies targeting CD52 and CD38 (isatuximab; Sarclisa, Sanofi-Aventis); CD3-CD38 bispecific antibodies (NCT05038644)[102]; and CAR T-cell therapy directed to CD7, CD4, CD5, anti-TRBC1, anti-CD1a, CCR9, CD38, and CAR natural killer (NK) cells for R/R disease after frontline therapy.[103] One novel approach is fratricide-resistant anti-CD7 CAR T-cell therapy (NS7CAR-T) using lentiviral transduction of peripheral T cells; it showed promising results in 60 patients, with 2-year OS and PFS rates of 63.5% and 53.7%, respectively, in R/R T-ALL, with a manageable safety profile.[104]

Conclusion

Immunotherapy has revolutionized the treatment of R/R ALL. Although rituximab was the first agent used in CD20-positive ALL, the advent of bispecific antibodies (eg, blinatumomab and InO) and CAR T-cell therapy is transforming the paradigm of ALL treatment. The incorporation of these antibodies into the treatment of newly diagnosed Ph-positive and Ph-negative B-ALL shows promise, but challenges remain in dose optimization, combination strategies (eg, with InO), route of administration, management of toxicities, and cost-effectiveness. Immunotherapy in T-ALL is still in development and mostly restricted to R/R disease. As therapies evolve, the therapeutic landscape will likely benefit not only younger and fitter patients but also older and frailer individuals. Immunotherapy has great potential to reduce and eventually largely replace the use of chemotherapy in ALL.

Disclaimer

This research was supported by the intramural research program of National Institutes of Health (NIH). The contributions of the NIH author, Ajoy Dias, MD, were made as part of their official duties as NIH federal employees, are in compliance with the agency policy requirements, and are considered works of the United States Government. However, the findings and conclusions presented in the paper are those of the author (Ajoy Dias), and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services.

Disclosures

Dr Dias has no disclosures. Dr Litzow has received research funding from AbbVie, Actinium, Amgen, Astellas, and Sanofi; has served on the speakers' bureaus of Amgen and BeOne Medicines; and has served on the Data Safety Monitoring Committee of Biosight.

References

1. Sasaki K, Jabbour E, Short NJ, et al. Acute lymphoblastic leukemia: a population-based study of outcome in the United States based on the surveillance, epidemiology, and end results (SEER) database, 1980-2017. *Am J Hematol*. 2021;96(6):650-658.
2. Brown PA, Shah B, Advani A, et al. Acute lymphoblastic leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021;19(9):1079-1109.
3. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007;109(3):944-950.
4. Oriol A, Vives S, Hernández-Rivas JM, et al. Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica*. 2010;95(4):589-596.
5. Oskarsson T, Söderhäll S, Arvidson J, et al. Relapsed childhood acute lymphoblastic leukemia in the Nordic countries: prognostic factors, treatment and outcome. *Haematologica*. 2016;101(1):68-76.
6. Grillo-López AJ, White CA, Varns C, et al. Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma. *Semin Oncol*. 1999;26(5)(suppl 14):66-73.
7. Pavlasova G, Mraz M. The regulation and function of CD20: an "enigma" of B-cell biology and targeted therapy. *Haematologica*. 2020;105(6):1494-1506.
8. Piccaluga PP, Arpinati M, Candoni A, et al. Surface antigens analysis reveals significant expression of candidate targets for immunotherapy in adult acute lymphoid leukemia. *Leuk Lymphoma*. 2011;52(2):325-327.
9. Raponi S, De Propris MS, Intoppa S, et al. Flow cytometric study of potential target antigens (CD19, CD20, CD22, CD33) for antibody-based immunotherapy in acute lymphoblastic leukemia: analysis of 552 cases. *Leuk Lymphoma*. 2011;52(6):1098-1107.
10. Maury S, Huguet F, Leguay T, et al. Adverse prognostic significance of CD20 expression in adults with Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia. *Haematologica*. 2010;95(2):324-328.
11. Thomas DA, O'Brien S, Jorgensen JL, et al. Prognostic significance of CD20 expression in adults with de novo precursor B-lineage acute lymphoblastic leukemia. *Blood*. 2009;113(25):6330-6337.
12. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer*. 2006;106(7):1569-1580.
13. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol*. 2010;28(24):3880-3889.
14. Hoelzer D, Gökbuget N. Chemoimmunotherapy in acute lymphoblastic leukemia. *Blood Rev*. 2012;26(1):25-32.
15. Maury S, Chevret S, Thomas X, et al; for GRAALL. Rituximab in B-lineage adult acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(11):1044-1053.
16. Marks DI, Kirkwood AA, Rowntree CJ, et al. Addition of four doses of rituximab to standard induction chemotherapy in adult patients with precursor B-cell acute lymphoblastic leukaemia (UKALL14): a phase 3, multicentre, randomised controlled trial. *Lancet Haematol*. 2022;9(4):e262-e275.
17. Barth MJ, Hernandez-Ilizaliturri FJ, Mavis C, et al. Ofatumumab demonstrates activity against rituximab-sensitive and -resistant cell lines, lymphoma xenografts and primary tumour cells from patients with B-cell lymphoma. *Br J*

Haematol. 2012;156(4):490-498.
18. Jabbour E, Richard-Carpentier G, Sasaki Y, et al. Hyper-CVAD regimen in combination with ofatumumab as frontline therapy for adults with Philadelphia chromosome-negative B-cell acute lymphoblastic leukaemia: a single-arm, phase 2 trial. *Lancet Haematol*. 2020;7(7):e523-e533.
19. Teeling JL, Mackus WJ, Wiegman LJ, et al. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol*. 2006;177(1):362-371.
20. Sasaki K, Kantarjian HM, Morita K, et al. Hyper-CVAD plus ofatumumab versus hyper-CVAD plus rituximab as frontline therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: a propensity score analysis. *Cancer*. 2021;127(18):3381-3389.
21. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med*. 2017;376(9):836-847.
22. Turner J, Schneider SM. Blinatumomab: a new treatment for adults with relapsed acute lymphocytic leukemia. *Clin J Oncol Nurs*. 2016;20(2):165-168.
23. Przepiorka D, Ko CW, Deisseroth A, et al. FDA approval: blinatumomab. *Clin Cancer Res*. 2015;21(18):4035-4039.
24. Jen EY, Xu Q, Schetter A, et al. FDA approval: blinatumomab for patients with B-cell precursor acute lymphoblastic leukemia in morphologic remission with minimal residual disease. *Clin Cancer Res*. 2019;25(2):473-477.
25. Pulte ED, Vallejo J, Przepiorka D, et al. FDA supplemental approval: blinatumomab for treatment of relapsed and refractory precursor B-cell acute lymphoblastic leukemia. *Oncologist*. 2018;23(11):1366-1371.
26. Rambaldi A, Ribera JM, Kantarjian HM, et al. Blinatumomab compared with standard of care for the treatment of adult patients with relapsed/refractory Philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia. *Cancer*. 2020;126(2):304-310.
27. Gökbuget N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood*. 2018;131(14):1522-1531.
28. Cabannes-Hamy A, Brissot E, Leguay T, et al. High tumor burden before blinatumomab has a negative impact on the outcome of adult patients with B-cell precursor acute lymphoblastic leukemia. A real-world study by the GRAALL. *Haematologica*. 2022;107(9):2072-2080.
29. Queudeville M, Stein AS, Locatelli F, et al. Low leukemia burden improves blinatumomab efficacy in patients with relapsed/refractory B-cell acute lymphoblastic leukemia. *Cancer*. 2023;129(9):1384-1393.
30. Aldoss I, Song J, Stiller T, et al. Correlates of resistance and relapse during blinatumomab therapy for relapsed/refractory acute lymphoblastic leukemia. *Am J Hematol*. 2017;92(9):858-865.
31. Köhnke T, Krupka C, Tischer J, Knösel T, Subklewe M. Increase of PD-L1 expressing B-precursor ALL cells in a patient resistant to the CD19/CD3-bispecific T cell engager antibody blinatumomab. *J Hematol Oncol*. 2015;8(1):111.
32. Braig F, Brandt A, Goebeler M, et al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. *Blood*. 2017;129(1):100-104.
33. Hathaway L, Sen JM, Keng M. Impact of blinatumomab on patient outcomes in relapsed/refractory acute lymphoblastic leukemia: evidence to date. *Patient Relat Outcome Meas*. 2018;9:329-337.
34. Jabbour E, Zugmaier G, Agrawal V, et al. Single agent subcutaneous blinatumomab for advanced acute lymphoblastic leukemia. *Am J Hematol*. 2024;99(4):586-595.
35. Bassan R, Chiaretti S, Della Starza I, et al. Up-front blinatumomab improves MRD clearance and outcome in adult Ph- B-lineage ALL: the GIMEMA LAL2317 phase 2 study. *Blood*. 2025;145(21):2447-2459.
36. Jabbour E, Short NJ, Jain N, et al. Hyper-CVAD and sequential blinatumomab for newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: a single-arm, single-centre, phase 2 trial. *Lancet Haematol*. 2022;9(12):e878-e885.
37. Boissel NHF, Graux C, Leguay T, et al. Frontline consolidation with blinatumomab for high-risk Philadelphia-negative acute lymphoblastic adult patients. Early results from the Graall-2014-QUEST phase 2 [ASH abstract 1232]. *Blood*. 2021;138(suppl 1).
38. Fleming S RJ, Bajel A, Venn N, Kwan J, Moore J, et al. Sequential blinatumomab with reduced intensity chemotherapy in the treatment of older adults with newly diagnosed Ph negative B-precursor acute lymphoblastic leukemia- interim analysis of the Australasian Leukemia and Lymphoma Group ALL08 study [ASH abstract 1234]. *Blood*. 2021;138(suppl 1).
39. Gupta S, Rau RE, Kairalla JA, et al. Blinatumomab in standard-risk B-cell acute lymphoblastic leukemia in children. *N Engl J Med*. 2025;392(9):875-891.
40. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008;111(4):1827-1833.
41. Rowe JM, Buck G, Burnett AK, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood*. 2005;106(12):3760-3767.
42. Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. *N Engl J Med*. 2024;391(4):320-333.
43. Litzow MR, Sun Z, Mattison RJ, et al. Consolidation with blinatumomab improves overall and relapse-free survival in patients with newly diagnosed B-cell acute lymphoblastic leukemia: impact of age and MRD level in ECOG-ACRIN E1910 [EHA abstract S115]. *Hemasphere*. 2023;7(suppl):e1944062.
44. Geyer MB, Hsu M, Devlin SM, Tallman MS, Douer D, Park JH. Overall survival among older US adults with ALL remains low despite modest improvement since 1980: SEER analysis. *Blood*. 2017;129(13):1878-1881.
45. Advani AS, Moseley A, O'Dwyer KM, et al. SWOG 1318: a phase II trial of blinatumomab followed by POMP maintenance in older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia. *J Clin Oncol*. 2022;40(14):1574-1582.
46. Goekbuget N, Stoltefuss A, Topp M, et al. Dose-reduced chemotherapy in sequence with blinatumomab for newly diagnosed older patients with B-precursor adult lymphoblastic leukemia (ALL): results of the ongoing GMALL bold trial [ASH abstract 3399]. *Blood*. 2021;138(suppl 1).
47. Jabbour E, Aldoss I, Fleming S, et al. Blinatumomab alternating with low-intensity chemotherapy (CT) treatment for older adults with newly diagnosed Philadelphia (Ph)- negative B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is well tolerated and efficacious: safety run-in results for the phase 3 randomized controlled Golden Gate study. *Blood*. 2022;140(suppl 1):6134-6136.
48. Clark EA, Giltiay NV. CD22: a regulator of innate and adaptive B cell responses and autoimmunity. *Front Immunol*. 2018;9:2235.
49. Jellusova J, Nitschke L. Regulation of B cell functions by the sialic acid-binding receptors siglec-G and CD22. *Front Immunol*. 2012;2:96.
50. Jin L, McLean PA, Neel BG, Wortis HH. Sialic acid binding domains of CD22 are required for negative regulation of B cell receptor signaling. *J Exp Med*. 2002;195(9):1199-1205.
51. Müller J, Obermeier I, Wöhner M, et al. CD22 ligand-binding and signaling domains reciprocally regulate B-cell Ca2+ signaling. *Proc Natl Acad Sci USA*. 2013;110(30):12402-12407.
52. DiJoseph JF, Armellino DC, Boghaert ER, et al. Antibody-targeted chemotherapy with CMC-544: a CD22-targeted immunoconjugate of calicheamicin for the treatment of B-lymphoid malignancies. *Blood*. 2004;103(5):1807-1814.
53. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med*. 2016;375(8):740-753.
54. Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol*. 2018;19(2):240-248.
55. Nasnas P, Jabbour E, Short N, et al. A phase II study of mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in older adults with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia: updated results and predictors for outcomes. *Blood*. 2022;140(suppl 1):11679-11682.
56. Stelljes M, Alakel N, Wasch R, et al. Inotuzumab ozogamicin induction followed by standard chemotherapy yields high remission rates and promising survival in older. *Blood*. 2022;140(suppl 1):510-512.
57. Chevallier P, Leguay T, Kim R, et al. Fractionated inotuzumab ozogamicin combined with low-intensity chemotherapy in older patients with newly diagnosed CD22+ Philadelphia chromosome (Ph)-negative B-cell precursor (BCP) acute lymphoblastic leukemia (ALL): results of the EWALL-INO study. *Blood*. 2022;140(suppl 1):6114-6116.
58. Wieduwilt MJ, Yin J, Kour O, et al. Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly diagnosed, Ph-negative, CD22- positive, B-cell acute lymphoblastic leukemia: Alliance A041703 [ASCO abstract 7006]. *J Clin Oncol*. 2023;41(suppl 16).
59. Nguyen D, Kantarjian HM, Short NJ, et al. Updated results from a phase II study of hyper-CVAD, with or without inotuzumab ozogamicin, and sequential blinatumomab in patients with newly diagnosed B-cell acute lymphoblastic leukemia [ASH abstract 4245]. *Blood*. 2023;142(suppl 1).
60. Short NJ, Jabbour E, Ravandi F, et al. The addition of inotuzumab ozogamicin

to hyper-CVAD plus blinatumomab further improves outcomes in patients with newly diagnosed B-cell acute lymphobastic leukemia: updated results from a phase II study [ASH abstract]. *Blood*. 2022;140(supp 1):8966-8968.
61. DeAngelo DJ, Yin J, Advani AS, et al. Addition of inotuzumab to a pediatric inspired chemotherapy regimen in young adult patients with B-cell acute lymphoblastic leukemia: findings from the Alliance A041501 phase 3 randomized trial [ASH abstract 308]. *Blood*. 2024;144(suppl 1).
62. McNeer JL, O'Brien MM, Rheingold SR, et al. A phase 3 randomized trial of inotuzumab ozogamicin for newly diagnosed high-risk B-ALL: a safety phase results from Children's Oncology Group Protocol AALL1732 [ASH abstract 3398]. *Blood*. 2021;131(suppl 1).
63. O'Brien MM, McNeer JL, Rheingold SR, et al. A phase 3 trial of inotuzumab ozogamicin for high-risk B-ALL: second safety results from Children's Oncology Group AALL1732 [ASCO abstract 10016]. *J Clin Oncol*. 2023;41(suppl 16).
64. Faderl S, Kantarjian HM, Talpaz M, Estrov Z. Clinical significance of cytogenetic abnormalities in adult acute lymphoblastic leukemia. *Blood*. 1998;91(11):3995-4019.
65. Wetzler M, Dodge RK, Mrózek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. *Blood*. 1999;93(11):3983-3993.
66. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. *Blood*. 2002;100(7):2357-2366.
67. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. *Blood*. 2009;113(19):4489-4496.
68. Larson RA. Management of acute lymphoblastic leukemia in older patients. *Semin Hematol*. 2006;43(2):126-133.
69. Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Haematologica*. 2015;100(5):653-661.
70. Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. *Blood*. 2014;123(6):843-850.
71. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. *Cancer*. 2015;121(23):4158-4164.
72. Sasaki K, Jabbour EJ, Ravandi F, et al. Hyper-CVAD plus ponatinib versus hyper-CVAD plus dasatinib as frontline therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: a propensity score analysis. *Cancer*. 2016;122(23):3650-3656.
73. Yilmaz M, Kantarjian H, Ravandi-Kashani F, Short NJ, Jabbour E. Philadelphia chromosome-positive acute lymphoblastic leukemia in adults: current treatments and future perspectives. *Clin Adv Hematol Oncol*. 2018;16(3):216-223.
74. Foà R, Bassan R, Vitale A, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. *N Engl J Med*. 2020;383(17):1613-1623.
75. Foà R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. *J Clin Oncol*. 2024;42(8):881-885.
76. Advani A, Moseley A, O'Dwyer K, et al. A phase 2 study of dasatinib, prednisone, and blinatumomab for older patients with Philadelphia- chromosome (Ph) positive or Ph-like acute lymphoblastic leukemia (ALL) (with dasatinib sensitive fusions/mutations) [ASH abstract 3397]. *Blood*. 2021;138(suppl 1).
77. Advani AS, Moseley A, O'Dwyer KM, et al. Dasatinib/prednisone induction followed by blinatumomab/dasatinib in Ph+ acute lymphoblastic leukemia. *Blood Adv*. 2023;7(7):1279-1285.
78. Kantarjian H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. *J Clin Oncol*. 2024;42(36):4246-4251.
79. Dargenio M, Bonifacio M, Chiaretti S, et al. Incidence, treatment and outcome of central nervous system relapse in adult acute lymphoblastic leukaemia patients treated front-line with paediatric-inspired regimens: a retrospective multicentre Campus ALL study. *Br J Haematol*. 2023;200(4):440-450.
80. Stock W, Martinelli G, Stelljes M, et al. Efficacy of inotuzumab ozogamicin in patients with Philadelphia chromosome-positive relapsed/refractory acute lymphoblastic leukemia. *Cancer*. 2021;127(6):905-913.
81. Jain N, Maiti A, Ravandi F, et al. Inotuzumab ozogamicin with bosutinib for relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia or lymphoid blast phase of chronic myeloid leukemia. *Am J Hematol*. 2021;96(8):1000-1007.
82. Elsallab M, Ellithi M, Hempel S, Abdel-Azim H, Abou-El-Enein M. Long-term response to autologous anti-CD19 chimeric antigen receptor T cells in relapsed or refractory B cell acute lymphoblastic leukemia: a systematic review and meta-analysis. *Cancer Gene Ther*. 2023;30(6):845-854.
83. Laetsch TW, Maude SL, Rives S, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. *J Clin Oncol*. 2023;41(9):1664-1669.
84. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.
85. Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet*. 2021;398(10299):491-502.
86. Shah BD, Ghobadi A, Oluwole OO, et al. Two-year follow-up of KTE-X19 in patients with relapsed or refractory adult B-cell acute lymphoblastic leukemia in ZUMA-3 and its contextualization with SCHOLAR-3, an external historical control study. *J Hematol Oncol*. 2022;15(1):170.
87. Shah BD, Cassaday RD, Park JH, et al. Impact of age, prior therapies, and subsequent transplant on long-term outcomes of adults with relapsed or refractory B-cell acute lymphoblastic leukemia (R/R B-ALL) treated with brexucabtagene autoleucel (brexu-cel) in ZUMA-3 [ASCO abstract 7023]. *J Clin Oncol*. 2023;41(suppl 16).
88. Roddie C, Sandhu KS, Tholouli E, et al. Safety and efficacy of obecabtagene autoleucel (obe-cel, AUTO1), a fast-off rate CD19 CAR, in relapsed/refractory adult B-cell acute lymphoblastic leukemia (r/r B-ALL): top line results of the pivotal FELIX study [ASCO abstract 7000]. *J Clin Oncol*. 2023;41(suppl 16).
89. FDA approves obecabtagene autoleucel for adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Posted November 8, 2024, 2024. Accessed June 27, 20245. https://shorturl.at/PIUIf.
90. Myers RM, Taraseviciute A, Steinberg SM, et al. Blinatumomab nonresponse and high-disease burden are associated with inferior outcomes after CD19-CAR for B-ALL. *J Clin Oncol*. 2022;40(9):932-944.
91. Park JH, Rivière I, Gonen M, et al. Long-term follow-up of CD19 CAR therapy in acute lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):449-459.
92. Schultz LM, Baggott C, Prabhu S, et al. Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: a Pediatric Real-World Chimeric Antigen Receptor Consortium report. *J Clin Oncol*. 2022;40(9):945-955.
93. Shah NN, Lee DW, Yates B, et al. Long-term follow-up of CD19-CAR T-cell therapy in children and young adults with B-ALL. *J Clin Oncol*. 2021;39(15):1650-1659.
94. Chen LY, Gong WJ, Li MH, et al. Anti-CD19 CAR T-cell consolidation therapy combined with CD19+ feeding T cells and TKI for Ph+ acute lymphoblastic leukemia. *Blood Adv*. 2023;7(17):4913-4925.
95. Yin Z, Lin Y, Liu D, Tong C, Liu S. CAR-T therapy as a consolidation in remission B-ALL patients with poor prognosis. *Cancer Rep (Hoboken)*. 2022;5(10):e1706.
96. Lu W, Wei Y, Cao Y, et al. CD19 CAR-T cell treatment conferred sustained remission in B-ALL patients with minimal residual disease. *Cancer Immunol Immunother*. 2021;70(12):3501-3511.
97. Niu J, Qiu H, Xiang F, et al. CD19/CD22 bispecific CAR-T cells for MRD-positive adult B cell acute lymphoblastic leukemia: a phase I clinical study. *Blood Cancer J*. 2023;13(1):44.
98. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood*. 2012;119(1):34-43.
99. Ravandi F, Aribi A, O'Brien S, et al. Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms. *J Clin Oncol*. 2009;27(32):5425-30.
100. Ronson A, Tvito A, Rowe JM. Treatment of relapsed/refractory acute lymphoblastic leukemia in adults. *Curr Oncol Rep*. 2016;18(6):39.
101. Bhatla T, Hogan LE, Teachey DT, et al. Daratumumab in pediatric relapsed/refractory acute lymphoblastic leukemia or lymphoblastic lymphoma: the DELPHINUS study. *Blood*. 2024;144(21):2237-2247.
102. Guru Murthy GS, Kearl TJ, Cui W, et al. A phase 1 study of XmAb18968, a CD3-CD38 bispecific antibody for the treatment of patients with relapsed/refractory acute leukemia and T cell lymphoblastic lymphoma [ASH abstract 4401]. *Blood*. 2021;138:4401.
103. Jing J, Ma Y, Xie Z, et al. Acute T-cell lymphoblastic leukemia: chimeric antigen receptor technology may offer a new hope. *Front Immunol*. 2024;15:1410519.
104. Zhang X, Yang J, Li J, et al. Analysis of 60 patients with relapsed or refractory T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma treated with CD7-targeted chimeric antigen receptor-T cell therapy. *Am J Hematol*. 2023;98(12):1898-1908.