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Novel monoclonal antibody-based treatment strategies in adults with acute lymphoblastic leukemia

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***Abstract*:** Adult acute lymphoblastic leukemia (ALL) has a poor overall survival compared with pediatric ALL where cure rates are observed in more than 90% of patients. The recent development of novel monoclonal antibodies targeting CD20, CD19, and CD22 has changed the long-term outcome of this disease, both in the frontline setting (e.g. rituximab) and for patients with relapsed/refractory disease (e.g. inotuzumab ozogamicin and blinatumomab). The CD3-CD19 bispecific T-cell-engaging antibody blinatumomab is also the first drug approved in ALL for patients with persistent or recurrent measurable residual disease, providing a new treatment paradigm for these patients. Several new agents are also in development that use novel constructs or target alternative surface epitopes such as CD123, CD25, and CD38. Herein, we review the role of monoclonal antibodies in adult ALL and summarize the current and future approaches in ALL, including novel combination therapies and the possibility of early incorporation of these agents into treatment regimens.

Keywords: acute lymphoblastic leukemia, blinatumomab, inotuzumab ozogamicin, monoclonal antibodies, rituximab

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Introduction

Acute lymphoblastic leukemia (ALL) represents 90% of all childhood leukemia and approximately 20% in adults.[1,2] In contrast with pediatric ALL, where the cure rate is more than 90% in most contemporary clinical trials, in adults, the disease is associated with a poor prognosis.[3,4] Despite high remission rates with multiagent chemotherapy, historically, long-term survival is about 40%.[4,5] In patients with relapsed/refractory disease treated with cytotoxic chemotherapy, the cure fraction declines even further to less than 10% with a median survival of approximately 6 months.[2,6]

The recent development of novel targeted therapies, such as monoclonal antibodies, has revolutionized the management of adults with ALL, changing the standard treatment paradigms.[7] Monoclonal antibodies can be classified into three main groups according to their construction: naked antibodies, conjugated antibodies, and bispecific antibodies. These agents bind to known surface cell antigens present on the ALL blasts and mediate cell death through a variety of mechanisms that are specific to their target antigens and construct. Naked antibodies bind directly to the surface cell antigen and mediate cell lysis through antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CDC) and induction of apoptosis. A variety of conjugated antibodies have also been developed that link a monoclonal antibody to a potent cytotoxin or radioisotope. These conjugated antibodies are internalized upon binding to the surface cell marker, leading to cell death by the release of the toxic payload. Bispecific, or bifunctional, antibodies engage two different target epitopes and consist of variable domains linked together forming a single-chain antibody, such as bispecific T-cell-engager antibodies, dual-affinity re-targeting antibodies and tandem single-chain variable fragments.[8] These antibodies lack an Fc region, are smaller in size, and

Table 1. Established and investigational monoclonal antibodies in acute lymphoblastic leukemia targeting CD20, CD19, and CD22.

Monoclonal antibody type	Surface target		
	CD20	**CD19**	**CD22**
Naked	Rituximab* Ofatumumab*		Epratuzumab
Conjugated		ADCT-402 (loncastuximab tesirine) SGN-CD19A (denintuzumab mafodotin) SAR3419 (coltuximab ravtansine)	Inotuzumab ozogamicin* Moxetumomab pasudotox* ADCT-602 (hLL2-Cys-PBD) 90Y-DOTA-epratuzumab
Bispecific		Blinatumomab* (anti-CD3-CD19)	

*United States Food and Drug Administration-approved antibodies for one or more hematological malignancies.

generally have a better tissue penetrance with less immunogenicity, although they have a shorter half-life than other types of antibody constructs.

All monoclonal antibodies currently approved for the treatment of ALL target the B-cell immunophenotype, whereas targeted therapies for T-cell ALL are still being investigated. The anti-CD20 antibody rituximab is widely used in front-line ALL treatment regimens due to multiple retrospective analyses as well as prospective randomized data showing a long-term survival benefit with its incorporation.[9–11] In relapsed/refractory ALL, an overall survival (OS) benefit has also been shown compared with the combination cytotoxic chemotherapy with the anti-CD22 antibody-drug conjugate (ADC) inotuzumab ozogamicin (INO) and the CD3-CD19 bispecific T-cell-engaging antibody blinatumomab, leading to full approval of both of these agents in 2017 by the United States (US) Food and Drug Administration (FDA).[11,12] Blinatumomab is also the only approved agent for the treatment of measurable residual disease (MRD) in ALL.[13]

Monoclonal antibodies against established targets

Most monoclonal antibodies in development for the treatment of ALL target CD20, CD19 or CD22 as these cell surface markers are highly expressed on ALL blasts. The CD20 antigen can be found in about 30 to 50% of B-cell precursor ALL, whereas CD19 and CD22 are present on the cell surface in over 90% of B-cell ALL.[14,15] A summary of the monoclonal antibodies directed at established targets of CD19, CD20, and CD22 that are currently in clinical use or in early phase clinical trials for patients with ALL is presented in Table 1.

Anti-CD20 antibodies

Rituximab. Rituximab was first extensively studied in non-Hodgkin lymphoma and Burkitt lymphoma and later evaluated in ALL.[16,17] Rituximab is a chimeric antibody against surface CD20 antigen with a murine variable region and a human Fc region.[18] Historically, the presence of the CD20 antigen (generally defined as CD20 expression ⩾20% on lymphoblasts) was associated with adverse prognosis in adult ALL.[9,14,18] In the pre-rituximab era, a retrospective analysis conducted at The University of Texas MD Anderson Cancer Center in patients with newly diagnosed B-cell ALL treated with either the vincristine, doxorubicin, and dexamethasone (VAD) or hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) regimens, showed higher incidences of relapse (61% *versus* 37%; $p < 0.01$) and inferior complete response duration (CRD) and OS (20% *versus* 55%; $p < 0.001$, and 27% *versus* 40%; $p = 0.03$) in CD20-positive compared with CD20-negative *de novo* precursor B-cell ALL.[14]

Rituximab in combination with the hyper-CVAD regimen was first assessed in a prospective study of *de novo* Philadelphia chromosome negative (Ph-negative) B-cell ALL and was compared with standard hyper-CVAD.[10] In CD20-positive patients, the addition of rituximab was associated with an increase in the CRD (67% *versus* 40%;

$p < 0.002$) and lower relapse rates (37% *versus* 60%; $p = 0.003$) but with no statistically significant difference in OS (61% *versus* 45%; p = nonsignificant). The benefit of incorporating rituximab was seen in patients younger than 60 years old (3-year OS 75% *versus* 47%; $p = 0.003$), whereas no improvement in CRD and OS was seen in patients ⩾60 years of age, likely due to a high rate of death in complete remission (CR) in this group. A similar benefit in CRD and OS was observed with the addition of rituximab to chemotherapy in younger patients (i.e. age 15–55 years) with CD20-positive B-cell ALL in the GMALL 07/2003 study, likely driven by higher MRD negativity rates in patients who received rituximab.[19]

The phase III, multicenter GRAALL-05 trial, randomized adult patients (18 to 59 years) with CD20-positive Ph-negative B-cell ALL to receive intensive chemotherapy with or without the addition of rituximab.[9] A total of 209 patients were included in the study (rituximab, $n = 105$; control, $n = 104$), with a median age of 40 years. CR rates and MRD negativity rates did not differ between the two arms. However, overall more patients underwent allogeneic hematopoietic stem cell transplantation (HSCT) in first CR in the rituximab group ($n = 36$, 34%) than in the control group ($n = 21$, 20%).

With a median follow up of 30 months, the event-free survival (EFS) was higher in the rituximab arm than in the control arm, with a 4-year EFS of 55% *versus* 43% ($p = 0.04$) and a lower 4-year incidence of relapse (25% *versus* 41%, $p = 0.02$). The 4-year OS was also higher in the rituximab group, although this did not reach statistical significance (61% *versus* 50%; $p = 0.10$). There was no increased in the incidence of severe adverse effects with the addition of rituximab; however, there was a significant decline in asparaginase-related allergic reactions in the rituximab group, which may have been driven by the immunologic effects of rituximab (2% *versus* 11%; $p = 0.002$).

Based on the results in this large randomized study, it is standard of care to add an anti-CD20 antibody such as rituximab to intensive chemotherapy in adults with CD20-positive precursor B-cell ALL who are <60 years of age. Although there is less compelling evidence for the benefit in older adults, at our institution and in many others, an anti-CD20 antibody is added to the treatment regimen of all CD20-positive patients with ALL, regardless of age and Philadelphia chromosome status, as this approach is associated with minimal (if any) added toxicity.

Ofatumumab. Ofatumumab is a second-generation anti-CD20 monoclonal antibody that binds to a proximal small loop epitope on the CD20 antigen, leading to more potent ADCC and CDC than rituximab.[20,21] In an ongoing phase II study, ofatumumab has been studied in combination with hyper-CVAD in patients newly diagnosed CD20-positive B-cell ALL.[22] Notably, CD20 expression was considered >1% for eligibility in this study. To date, 68 patients have been treated, with a median age of 41 years (range, 18–71 years). Overall, 63% (39/62) of patients achieved MRD negativity by flow cytometry at the time of CR and 93% (62/67) at any time throughout therapy. With a median follow up of 27 months, the 2-year OS and CRD rates were 81% and 71%, respectively. When stratified by CD20 expression <20% and ⩾20%, there was no difference in survival. However, there was a trend toward improved OS in patients with CD20 expression ⩾20% treated with ofatumumab plus hyper-CVAD compared with a historical cohort treated with rituximab plus hyper-CVAD ($p = 0.14$).[23] Longer follow up will be needed to determine whether ofatumumab improves long-term outcomes compared with rituximab in this population.

Blinatumomab (anti-CD19 antibody)

Blinatumomab is a CD3-CD19 bispecific T-cell-engaging antibody that consists of a small single-chain peptide connecting two single-chain variable fragments and binds both CD19 on B-cells and CD3 on T-cells.[7,24] Due to its construction, it has a short half-life and requires continuous infusion. Upon binding to its CD19 target, blinatumomab can activate T-cells without the need for any additional costimulatory signals and leads to polyclonal expansion of cytotoxic CD8-positive T-cells, T-cell activation, and cell lysis of CD19-positive lymphoblasts through cytokine and cytotoxic granules release.[21,24,25]

Blinatumomab in relapsed/refractory ALL. In early phase I and II studies in patients with relapsed or refractory Ph-negative B-cell ALL, blinatumomab was shown to have significant antileukemic activity with manageable toxicity, consisting primarily of neurotoxicity and cytokine release syndrome (CRS). These studies reported CR/CR with partial

hematologic recovery (CRh) rates of ranging from 43 to 54%, MRD negativity in 82 to 84% of patients, and a median OS of 6.1 to 10.6 months with single-agent blinatumomab.[26–29]

The phase III multicenter TOWER study randomized patients with relapsed/refractory B-cell ALL patients in a 2:1 ratio to receive blinatumomab *versus* multiagent cytotoxic chemotherapy.[30] Blinatumomab was given as a 28-day continuous infusion at a dose of 9 μg/day for the first week of induction and then 28 μg/day thereafter (cycle = 42 days), with dexamethasone prophylaxis for patients with a high disease burden. Of the 405 patients enrolled, 56% had received two or more prior therapies, and 35% had undergone prior allogeneic HSCT.

Blinatumomab was superior to chemotherapy, achieving higher CR rates (34% *versus* 16%; $p < 0.001$), a higher 6-month EFS rate (31% *versus* 12%; $p < 0.001$) and longer median OS (7.7 *versus* 4 months; $p = 0.001$), with significant benefit observed in patients treated with blinatumomab regardless of age, number of previous therapies, previous HSCT, or bone marrow blast percentage. Grade 3 or higher CRS and neurologic events occurred in 5% and 9% of patients, respectively.

Blinatumomab has also been shown to be active and well tolerated in patients with relapsed/refractory Ph-positive ALL.[31] In the phase II ALCANTARA study, 45 patients with relapsed/refractory Ph-positive ALL who failed or were intolerant to at least one second-generation or later tyrosine kinase inhibitor (TKI), received blinatumomab at standard dosing. The median age was 55 years (range, 23–78 years). This was a very poor risk population, with 38 patients (84%) who had received two or more prior TKIs, 23 (51%) who had received prior ponatinib, 20 (44%) who had undergone prior HSCT, and 10/37 (27%) with a T315I mutation.

After two cycles, 36% of the patients achieved CR/CRh, regardless of prior TKI exposure or T315I mutation status, with 88% of responders achieving MRD negativity by BCR-ABL quantification by real-time polymerase chain reaction (PCR) with a sensitivity of 10^{-5}, and 44% being able to undergo HSCT. There was a trend toward a higher CR/CRh rate for patients with a lower tumor burden (i.e. bone marrow blasts <50%), compared with those with a higher burden, with CR/CRh rates of 64% and 27%, respectively. The median relapse-free survival (RFS) and OS were 6.7 months and 7.1 months, respectively. Notably, although the response rate of blinatumomab is similar to that achieved with ponatinib in patients with relapsed/refractory Ph-positive ALL, the duration of remission with blinatumomab compares favorably with single-agent ponatinib, which has a median duration of remission of only 3 months and a 1-year progression-free survival (PFS) rate of only 7% in a similar population.[32]

Based on the results of these phase II and phase III studies, blinatumomab became the first monoclonal antibody for ALL to be approved by the US FDA in December 2014, with a full approval in July 2017 for the treatment of relapsed/refractory B-cell ALL, regardless of Philadelphia chromosome status.[29–31,33,34]

Blinatumomab in MRD-positive ALL. Blinatumomab has also been evaluated in patients with only MRD-positive disease in several phase II trials. In one study, 21 patients with B-cell ALL and positive MRD as detected by quantifiable PCR at a level of $\geqslant 10^{-4}$ were treated with blinatumomab.[35,36] Blinatumomab was given at a dose of 15 μg/m^2/day in continuous infusion for 4 weeks, followed by a 2-week break (i.e. 42-day cycle). Of 20 evaluable patients, 16 (80%) achieved MRD negativity after one cycle of therapy, independent of pretreatment MRD burden. Overall, nine patients were bridged to HSCT after blinatumomab therapy. With a median follow up of 33 months, RFS was 61%.

In the phase II BLAST trial, patients with B-cell ALL in CR with persistent or recurrent MRD positivity (MRD $\geqslant 10^{-3}$ by PCR or flow cytometry) received up to four cycles of blinatumomab at a dose of 15 μg/m^2/day for 4 weeks, followed by 2 weeks of no therapy.[13,37] A total of 116 patients were enrolled, with a median age of 45 years (range, 18–76 years). A total of 41 patients (35%) were in second or third CR, and 55 patients (47%) had a high MRD burden (i.e. above 10^{-2}). MRD negativity was achieved in 78% of patients after the first cycle and 88% overall. MRD negativity was associated with a higher RFS (23.6 *versus* 5.7 months) and OS (38.8 *versus* 12.5 months)

compared with MRD-positive patients, with a better survival seen for patients in first remission. Overall, CRS was reported in 3% of patients and neurologic side effects of any grade in 53% of patients, with grade 3 and 4 events in 10% and 3%, respectively. There was a decline in adverse events after subsequent cycles of blinatumomab. A post hoc analysis showed no significant difference in RFS for patients with or without HSCT after blinatumomab, raising the important question of the role of HSCT for these patients after they convert to MRD negativity. With a median follow up of 53.1 months, median OS was 36.5 months, with a plateau after 36 months, suggesting that many of these patients may be cured.

Based on these results blinatumomab became the first therapy approved by the US FDA for MRD-positive B-cell ALL in March 2018.[38] The availability of an active agent for patients with MRD-positive disease has revolutionized the way these patients are treated and provides an important treatment option rather than immediate HSCT, which historically was the only therapeutic option available for these patients.[39]

Inotuzumab ozogamicin (anti-CD22 antibody)

INO is an ADC, consisting of an anti-CD22 humanized monoclonal antibody bound to the potent alkylating agent calicheamicin, which is produced by *Micromonospora echinospora*. Upon binding to CD22 on the cell surface, INO is internalized and calicheamicin is released into the target cell. Calicheamicin then binds to double-stranded DNA causing DNA breaks and cell death by apoptosis.[40,41]

In the early phase II clinical trial, patients with relapsed or refractory CD22-positive B-cell ALL were treated with INO 1.8 mg/m^2 once every 3–4 weeks.[40] A total of 49 patients were treated with a median age of 36 years (range, 6–80 years). The overall response rate was 57%, and the median OS was 5.1 months. MRD negativity, as assessed by flow cytometry with a sensitivity of 0.01%, was achieved in 63% of patients. The median duration of response was 6.3 months. The most frequent side effects associated with INO therapy were fever, hypotension, increased liver enzymes, and thrombocytopenia. Among patients who underwent subsequent HSCT, 23% developed veno-occlusive disease (VOD), with the majority of patients having been exposed to conditioning regimens with clofarabine and thiotepa. Subsequently, additional studies demonstrated that the use of INO at a fractionated weekly dose of 0.8 mg/m^2 on day 1 followed by 0.5 mg/m^2 on day 8 and 15 was associated with a lower incidence of VOD in post-HSCT patients, as well as decreased rates of fever and hypotension, with no difference in response rates and duration of response.[42,43] Thus, weekly administration of INO is generally preferred to monthly dosing, as this schedule balances safety and efficacy.

In the phase III randomized, INO-VATE study, 218 patients with relapsed/refractory CD22-positive ALL were assigned in a 1:1 ratio to receive either INO or combination cytotoxic chemotherapy.[12] INO was given at a 1.8 mg/m^2 per cycle in a fractionated weekly schedule (0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15 per cycle). The chemotherapy regimens were either FLAG regimen (fludarabine, cytarabine and granulocyte colony-stimulating factor), a high-dose cytarabine-based regimen, or cytarabine plus mitoxantrone.

The CR/CR with incomplete hematologic recovery (CRi) and MRD negativity rate was significantly higher in the INO arm with CR/CRi rates of 81% *versus* 29% ($p < 0.001$) and an MRD negativity rate by flow cytometry (sensitivity = 0.01%) of 78% *versus* 28% ($p < 0.001$), respectively. The median duration of response was 4.6 months and 3.1 months for INO and chemotherapy, respectively. Compared with the chemotherapy group, more patients who received INO were able to undergo HSCT (41% *versus* 11%; $p < 0.001$). The median PFS for INO and for combination chemotherapy was 5 *versus* 1.8 months ($p < 0.001$), and the median OS was 7.7 *versus* 6.7 months ($p = 0.04$), respectively. Significantly higher remission rates were seen with INO in all subgroups, regardless of bone marrow blasts percentage, CD22 expression, previous HSCT or karyotype, except for patients with t(4:11) Ph-positive ALL who did not preferentially benefit from either therapy.

Hepatotoxicity was a frequent event in patients treated with INO, with increased aspartate aminotransferase, alanine aminotransferase and

bilirubin levels of any grade in 20%, 14% and 15% of patients, respectively. Of note, VOD was reported in 15 patients (11%) in the INO group, with most cases (10 of 15 patients) occurring after HSCT and with a median time to development of 16 days (range, 3–39 days). Subsequent multivariate analysis showed that use of dual-alkylating conditioning regimens was associated with a higher incidence of post-HSCT VOD ($p = 0.04$), similar to the observations in earlier phase trials. Based on the higher response rates and improvement in OS observed in the INOVATE phase III trial, INO was approved by the US FDA for the treatment of relapsed/refractory B-cell ALL in August 2017.[44] The efficacy of single-agent INO for MRD-positive ALL is currently being evaluated in two clinical trials (ClinicalTrials.gov identifiers: NCT03610438 and NCT03441061).

Combination trials with blinatumomab and inotuzumab ozogamicin

Given the promising clinical activity of monoclonal antibodies such as INO and blinatumomab, early addition of these agents to the frontline may lead to longer remission rates and OS, while potentially decreasing the amount of cytotoxic chemotherapy required to achieve durable responses. Such regimens may improve tolerability and decrease treatment-related morbidity and mortality. Similarly, in the relapsed/refractory setting, combination studies are ongoing in order to improve upon the outcomes achieved with single-agent monoclonal antibody-based therapy by achieving deeper responses, which have been shown to improve outcomes, particularly for patients in first salvage.[45] While HSCT in the second remission is currently considered the standard of care for adults with ALL, it is possible that novel, effective combination regimens may obviate the need for HSCT in this population. Table 2 summarizes major combination studies in B-cell ALL in which results are available.

Ph-negative ALL

To improve upon the outcomes observed with single-agent INO, a phase I/II study was conducted evaluating the safety and efficacy of the combination of INO with low-intensity chemotherapy in patients with relapsed/refractory Ph-negative CD22-positive ALL.[54] The chemotherapy was a dose-reduced hyper-CVAD regimen with omission of the anthracycline (i.e. mini-hyper-CVD). With a 50% dose reduction of cyclophosphamide and dexamethasone in odd cycles and a 75% dose reduction of methotrexate and an 83% dose reduction of cytarabine in even cycles. Patients received eight cycles of mini-hyper-CVD, followed by 3 years of POMP (prednisone, vincristine, methotrexate, and 6-mercaptopurine) maintenance. INO was administered on day 3 of the first four cycles of mini-hyper-CVD. Initially, an INO dose of 1.8 mg/m^2 was given in cycle 1, followed by a dose reduction to 1.3 mg/m^2 in cycles 2–4. After cases of VOD were observed, the protocol was amended to use lower doses of INO, initially to 1.3 mg/m^2 in cycle 1 and 1.0 mg/m^2 for cycles 2–4, and most recently, at a fractionated dose of 0.6 mg/m^2 on day 2 and 0.3 mg/m^2 on day 8 in cycle 1 and 0.3 mg/m^2 on day 2 and 8 of cycles 2–4. With this most recent amendment, the total number of mini-hyper-CVD + INO cycles was also decreased to four, followed by four cycles of blinatumomab consolidation. Patients also now receive approximately 18 months of maintenance, composed of alternating blocks of three cycles of POMP and one cycle of blinatumomab.

In the most recent follow up, 89 patients with relapsed/refractory Ph-negative B-cell ALL have been treated with the combination of mini-hyper-CVD + INO, with or without blinatumomab.[46] The median age was 36 years (range, 9–87 years). A total of 57 patients (64%) were in first salvage; 19 (21%) had undergone prior HSCT. The ORR was 79% for the entire cohort, with an ORR of 91% for patients in first salvage. Overall, 82% of patients achieved MRD negativity by 6-color flow cytometry with a sensitivity of $\leq$0.01%. The median CRD and OS were 30 months and 14 months, respectively. The overall rate of VOD was 11%, with 9/68 patients (15%) in the original INO schedules developing VOD and no new cases reported after the amendment to use weekly fractionated INO. Survival was particularly promising in patients in first salvage, where a median OS of 25 months was achieved.[47] In a comparison of this regimen with historical data with single-agent INO, OS appears to be significantly improved with the mini-hyper-CVD + INO $\pm$ blinatumomab regimen (median OS: 14 months *versus* 6 months, $p = 0.001$).

Table 2. Monoclonal antibody combination studies in frontline and relapsed/refractory B-cell ALL.

	Population	*N*	Age (years) median [range]	CR/CRi rate	MRD negativity by flow cytometry	CRD	RFS	OS
Relapsed/refractory								
INO + mini-hyper-CVD ± blinatumomab [46,47]	R/R Ph−	84	35 (9–87)	80%	80%	49% at 3 y	-	33% at 3 y
INO + bosutinib[48]	R/R Ph +	14	62 (19–74)	79%	73%	—	—	8.2 months (median)
Frontline								
Blinatumomab + POMP[49]	Ph− (age ⩾ 65 y)	31	75 (66–84)	66%	92%	—	—	65% at 1 y
Hyper-CVAD + blinatumomab[50]	Ph− (age ⩾ 14 y)	17	43 (20–59)	100%	93%	—	77% at 1 y	90% at 1 y
INO + mini-hyper-CVD ± blinatumomab [51,52,53]	Ph− (age ⩾ 60 y)	58	68 (60–81)	98%	95%	77% at 3 y	—	54% at 3 y

CR, complete remission; CRD, complete response duration; CRi, complete remission with incomplete hematological recovery; hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; hyper-CVD, hyperfractionated cyclophosphamide, vincristine, and dexamethasone; INO, inotuzumab ozogamicin; MRD, minimal residual disease; OS, overall survival; Ph+, Philadelphia chromosome positive; Ph−, Philadelphia chromosome negative; POMP, prednisone, vincristine, methotrexate, and 6-mercaptopurine; RFS, relapse-free survival; R/R, relapsed/refractory; y, years.

This same regimen has also been explored in patients 60 years or older with newly diagnosed Ph-negative B-cell ALL.[51,52] Notably, the treatment of older adults is particularly challenging due to their poor tolerance to chemotherapy and the increased incidence of high-risk disease compared with younger patients.[55] In the most recent update, 68 patients were treated, with a median age of 68 years (range, 60–81 years). The ORR was 98%, with no early deaths observed. MRD negativity by flow cytometry was achieved in 78% of patients after one cycle and in 95% of patients at any time during the course of therapy. The 3-year CRD and OS were 74% and 54%, respectively. A propensity score analysis with 1:1 matching to a similar population of older patients with newly diagnosed B-cell ALL treated with hyper-CVAD demonstrated superior OS and EFS for the INO- and blinatumomab-containing regimen, with 3-year OS rates of 63% *versus* 34% ($p = 0.001$) and 3-year EFS rates of 64% *versus* 34% ($p = 0.001$), respectively.[53] These results are the best described in the literature for this older population in ALL and may represent a new standard of care.

In newly diagnosed older patients (age ⩾ 65 years) with Ph-negative B-cell ALL, the combination of frontline therapy with blinatumomab (four to five cycles) follow by POMP was recently evaluated in a phase II trial.[49] In an interim analysis, 31 patients were enrolled with a median age of 75 years (range, 66–84 years). The treatment was well tolerated with only one patient developing grade 3 CRS and one patient with grade 3 neurotoxicity, and no early death reported. MRD negativity by flow cytometry was achieved in 92% (12/13) of responders after one cycle. The 1-year OS and disease-free survival at 1 year were 65% and 56%, respectively.

For younger patients (i.e. age <60 years) with newly diagnosed Ph-negative B-cell ALL, a phase II study is currently being conducted evaluating the sequential administration of hyper-CVAD and blinatumomab.[50] Patients received four cycles of hyper-CVAD follow by four cycles of blinatumomab and then approximately 16 months maintenance with standard POMP alternating with blinatumomab in cycles 4, 8 and 12 of maintenance. To date, 19 patients have been treated

with a median age of 42 years (range, 18–59 years). The ORR was 100%, and 93% of patients achieved MRD negativity by flow (sensitivity = 0.01%) after one cycle of chemotherapy. With a median follow up of 17 months, only one death was observed in a patient who developed post-HSCT complications. The 1-year OS and RFS were 93% and 75%, respectively. Longer follow up will be needed to determine whether decreasing the chemotherapy and adding blinatumomab to the frontline setting can improve outcomes compared with standard hyper-CVAD for these younger patients. Future studies in younger patients incorporating INO in the frontline setting, including in combination with blinatumomab, are warranted.

Ph-positive ALL

Blinatumomab was shown in the phase II ALCANTARA study to be highly effective in patients with Ph-positive ALL.[31] Thus, several studies are evaluating it in combination with BCR-ABL TKIs for patients with relapsed/refractory Ph-positive ALL, as well as in the frontline setting. In a retrospective study of 13 patients with relapsed/refractory Ph-positive ALL and chronic myeloid leukemia (CML) in lymphoid blast phase with either overt relapse or MRD-only disease received treatment with blinatumomab in combination with a TKI (ponatinib, dasatinib, or bosutinib).[56,57] Overall, two patients had a T315I mutation. The combination was shown to be effective with 57% (4/7) of patients achieving CR/CRi, 75% (6/8) achieving a complete cytogenetic response, and 77% (10/13) achieving complete molecular response. With a median follow up of 10 months, the median duration of response was 8 months and the median OS was not reached. Overall, the 1-year OS rate was 74% (75% for patients treated with blinatumomab plus ponatinib). The combination was well tolerated, with grade 2 CRS only seen in three patients. Based on these promising preliminary data, blinatumomab in combination with various TKIs is currently under investigation.

A phase II study of the combination of blinatumomab and ponatinib for older patients with newly diagnosed Ph-positive B-cell ALL and adults of any age with relapsed/refractory Ph-positive ALL is ongoing (ClinicalTrials.gov identifier: NCT03263572). Phase II studies with blinatumomab and dasatinib for patients 65 years or older with newly diagnosed Ph-positive ALL (ClinicalTrials.gov identifier: NCT02143414) and for patients with relapsed/refractory Ph-positive ALL (ClinicalTrials.gov identifier: NCT02744768) are ongoing. Table 3 summarizes ongoing clinical trials with monoclonal antibodies with combination therapies.

Ponatinib is the most potential commercially available TKI for patients with Ph-positive ALL[58]; however, due to its association with hepatotoxicity, its potential for combination with INO is limited. Therefore, studies have investigated INO in combination with less hepatotoxic TKIs, particularly bosutinib. In a phase I/II trial, patients with relapsed/refractory Ph-positive ALL or lymphoid blast phase CML, bosutinib in combination with INO was shown to be well tolerated and effective.[48] Notably, patients with T315I mutations were not eligible for this study. Patients received bosutinib at a dose of 300–500 mg with weekly INO at a dose of 0.5–0.8 mg/m^2 on days 1, 8 and 15, given in 4-weekly cycles. A total of 14 patients were treated with a median age of 62 years. Overall, 79% of patients achieved CR/CRi, with 91% of responders achieving a complete cytogenetic remission and 73% achieving MRD negativity by flow cytometry. BCR-ABL was undetectable in 55% (6/11) of responders. The median OS was 8.2 months and median EFS was 8.1 months.

Novel agents in early phases of development

Several new monoclonal antibodies are in the early phases of development, most of them targeting the three main antigens (CD19, CD20 and CD22) but also CD25, CD123, and CD38. The vast majority of conjugated drug antibodies bind to different cytotoxins, with the exception of the radioimmunoconjugate, 90Y-DOTA-epratuzumab, the naked antibody daratumumab, and the bispecific CD3/CD123 antibody XmAB12045. Table 4 summaries active early phase clinical trials with monoclonal antibodies in ALL.

The anti-CD22 antibodies epratuzumab, moxetumomab pasudotox, and 90Y-DOTA-epratuzumab, as well as the anti-CD19 ADCs coltuximab ravtansine (SAR3419) and denintuzumab mafodotin (SGN-CD19A), have all showed activity in adult relapsed/refractory B-cell ALL. However, the responses were modest, and these constructs are

Table 3: Summary of ongoing clinical trials with monoclonal antibodies with combination therapies in B-cell ALL.

Monoclonal antibody	Combination treatment	Trial Phase	Population	Age (years)	Clinicaltrials.gov Identifier
Relapsed/Refractory					
Blinatumomab	Pembrolizumab	I/II	Ph- and Ph+	⩾ 18	NCT03160079
Blinatumomab	Nivolumab ± ipilimumab	I	CD19+ Ph- and Ph+ ALL/MPAL	> 21	NCT02879695
Blinatumomab	Ibrutinib	II	Ph- and Ph+	⩾ 18	NCT02997761
Blinatumomab	mini-hyper-CVD	II	Ph-	⩾18	NCT03518112
Blinatumomab	Dasatinib	II	Ph+ and Ph-like+DSMKF	⩾ 65	NCT02143414
Blinatumomab	Ponatinib	II	Ph+ ALL/AP-CML/BP-CML	⩾ 18	NCT03263572
INO	CVP	I	CD22+ Ph- ALL/BAL/BL and Ph+ ALL	⩾ 18	NCT01925131
INO	Bosutinib	I/II	CD22+ Ph+	⩾ 18	NCT02311998
INO	mini-hyper-CVD	I/II	Ph-	All ages	NCT01371630
Frontline					
Blinatumomab	Nivolumab ± ipilimumab	I	CD19+ ALL/MPAL	⩾ 60	NCT02879695
Blinatumomab	Chemotherapy	II	Ph- CD19+	18-65	NCT03367299
Blinatumomab	AIEOP-BFM ALL 2017	III	Ph- ALL/MPAL	<18	NCT03643276
Blinatumomab	PETHEMA	II	Ph- CD19+	18-55	NCT03523429
Blinatumomab	HOVON146ALL	II	CD19+ Ph- ALL/MPAL and Ph+	18-70	NCT03541083
Blinatumomab	HCVAD	II	Ph-	⩾ 14	NCT02877303
Blinatumomab	Dasatinib	II	Ph+	⩾ 65	NCT02143414
Blinatumomab	Ponatinib	II	Ph+	⩾ 60	NCT03263572
Blinatumomab	Dasatinib	II	Ph+ ALL/ BP-CML	⩾ 18	NCT02744768
Blinatumomab	POMP	II	Ph-	⩾ 65	NCT02143414
INO	mini-HCVD	I/II	Ph-	⩾ 60	NCT01371630
INO	EWALL	II	Ph- CD22+	⩾ 55	NCT03249870
INO	HCVAD	II	Ph-	⩾ 16	NCT03488225
INO	Chemotherapy	III	CD22+ Ph-	18-39	NCT03150693

Abbreviations: INO = inotuzumab ozogamicin, Ph- = Philadelphia chromosome-negative, Ph+ = Philadelphia chromosome-positive, ALL = acute lymphoblastic leukemia, MPAL = mixed phenotype acute leukemia, Ph-like+DSMKF = Philadelphia-like with dasatinib-sensible mutations or kinase fusions, AP-CML= accelerated phase chronic myeloid leukemia, BP-CML= blast phase chronic myeloid leukemia, BAL= biphenotypic acute leukemia, BL= Burkitt leukemia, HCVAD, hyperfractionated cyclophophamide, vincristine, doxorubicin and dexamethasone; CVP, cyclophosphamide, vincristine and prednisone; POMP, 6-mercaptopurine, vincristine, methotrexate and prednisone; the other abbreviations are usually referred to by their abbreviations.

Table 4. Novel monoclonal antibody constructs in early clinical development in B-cell ALL.

Monoclonal antibody	Target	Type of antibody	Trial phase	Population	Age (years)	Clinicaltrials.gov identifier
ADCT-602	CD22	Conjugated	I/II	R/R CD22+	⩾18	*NCT03698552*
ADCT-402	CD19	Conjugated	I	R/R	⩾12	*NCT02669264*
Denintuzumab (SGN-CD19A)	CD19	Conjugated	I	R/R Ph– ALL, B-LBL, BL/Ph+	>1	*NCT01786096*
Camidanlumab tesirine (ADCT-301)	CD25	Conjugated	I	R/R CD25+ AML/ ALL	⩾18	*NCT02588092*
IMGN632	CD123	Conjugated	I	R/R CD123+ heme malignancies	⩾18	*NCT03386513*
XmAb14045	CD3-CD123	Bispecific	I	R/R CD123+ heme malignancies	⩾18	*NCT02730312*
Daratumumab	CD38	Naked	II	R/R Ph– B-ALL and T-ALL	⩽30	*NCT03384654*

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BL, Burkitt's lymphoma; B-LBL, B-cell lymphoblastic lymphoma; heme, hematologic; NCT, ClinicalTrials.gov identifier; Ph–, Philadelphia chromosome negative; Ph+, Philadelphia chromosome positive; R/R, relapsed/refractory; T-ALL, T-cell acute lymphoblastic leukemia.

unlikely to play a significant role in the treatment of ALL and are no longer being evaluated in adult ALL.[59–63] However, the monoclonal antibody anti-CD20 obinutuzumab (GA101) has demonstrated preclinical activity in rituximab-resistant Burkitt lymphoma and pre-B-ALL-engrafted mice, with a higher intensity of ADCC and direct apoptosis than other anti-CD20 antibodies; to date there are no clinical trials ongoing in ALL.[21]

In contrast, trials with other novel monoclonal antibodies such as ADCT-602 (anti-CD22 ADC), ADCT-402 (anti-CD19 ADC), ADCT-301 (anti-CD25 ADC), and XmAB14045 (CD3/CD123 bispecific antibody) are ongoing in adult ALL. Recently a phase I dose escalation study with ADCT-402 (loncastuximab tesirine), an ADC with tesirine in relapsed/refractory B-cell ALL, patients has been completed (ClinicalTrials.gov identifier: NCT02669264). Patients received either weekly infusions on day 1, 8 and 15 or a single dose every 3 weeks with dose escalation until the maximum tolerated dose was identified, followed by an expansion for all patients with the recommended dose. The interim data has shown that ADCT-402 has antileukemic activity in heavily pretreated patients, with 2/23 patients achieving CR with negative MRD, and was well tolerated with no drug-limiting toxicities.[64] Patient accrual is ongoing.

These novel monoclonal antibodies vary in their properties and their potential advantages compared with currently available therapies. For example, there is much interest in the development of effective CD19-targeting therapies, such as ADCT-402, that have greater ease of administration than blinatumomab (i.e. intermittent *versus* continuous infusion). There is also hope that the incidence of hepatotoxicity and VOD with the anti-CD22 ADC ADCT-602 will be less than seen with INO given its use of a pyrrolobenzodiazepine dimer toxin, rather than a calicheamicin toxin. However, further studies are needed to determine the safety and efficacy of these new monoclonal antibodies.

Daratumumab is a human monoclonal antibody against CD38, which is highly expressed in T-cells and thymocytes but has low expression in normal lymphoid and myeloid cells. Recent preclinical data and case reports have shown the antileukemic effect of daratumumab in relapsed/refractory T-cell and CD38-positive ALL by induction of apoptosis *via* ADCC and CDC.[65–67] Daratumumab

was particularly effective against xenograft models with early T-cell precursor ALL and low disease burden.[65] In a series of cases, in relapsed/refractory B-cell and T-cell ALL patients, weekly daratumumab at a 16 mg/kg dose for a total of 8 weeks, alone and in combination with vincristine or steroids demonstrated an antileukemic effect.[66–68] CR with MRD negativity by flow cytometry was reported after therapy with daratumumab in heavily pretreated patients with both Ph-positive ALL and T-cell ALL.[68] A phase II study to evaluate the effectiveness and safety of daratumumab in pediatric and young adults with relapsed/refractory precursor B-cell or T-cell ALL will start enrollment soon (ClinicalTrials.gov identifier: NCT03384654). An effective monoclonal antibody for patients with T-cell ALL is particularly needed, as there are currently no US FDA antibodies for this ALL subtype, and options for relapsed/refractory disease are limited.

Both ADCT-301 (camidanlumab tesirine), an ADC against CD25 attached to a pyrrolobenzodiazepine dimer cytotoxin, and XmAB14045, a bispecific CD3/CD123 antibody, have shown antileukemic activity in phase I studies in relapsed/refractory acute leukemias.[69–71] However, both CD25 and CD123 being uncommonly express in ALL, so it is unclear how much of a role these agents will play in the future of ALL.

Another exciting approach is the combination of monoclonal antibodies with checkpoint inhibitors. It has been established that the presence of high levels of regulatory T-cells is associated with an inferior response to blinatumomab by suppression of T-cell proliferation.[72] The combination of a programmed cell death (PD)-1 inhibitor with blinatumomab may overcome this mechanism of resistance, by restoration of T-cell proliferation.[73] The early results of the phase I trial with blinatumomab and nivolumab, with or without the cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibitor ipilimumab, showed promising results, with four out of five patients achieving CR with MRD negativity by flow cytometry.[74] To date, various clinical trials are evaluating the addition of checkpoint inhibitors in ALL, such as the combination of blinatumomab, nivolumab, and ipilimumab in relapsed/refractory and frontline ALL (ClinicalTrials.gov identifier: NCT02879695) and blinatumomab and pembrolizumab in relapsed/refractory ALL (ClinicalTrials.gov identifier: NCT03160079).

Future directions

While the development of monoclonal antibodies for the treatment of ALL has undoubtedly improved the outcomes of adults with this disease, it has also raised many important questions in the field. Perhaps one of the most pressing questions is how these agents should be optimally combined, with and without chemotherapy, in both the frontline and relapsed/refractory settings. Particularly for frontline ALL treatment, the hope is that early integration of highly active agents such as INO or blinatumomab can reduce the need for intensive chemotherapy, and thus decrease treatment-related mortality, while still maintaining (or improving) efficacy. Initial studies of combinations of low-intensity plus INO, with or without blinatumomab, are promising in both older patients in the frontline setting and in relapsed/refractory disease.[46,47,51,52,75] In patients with Ph-positive ALL, retrospective studies have shown the safety and efficacy of combining blinatumomab with TKIs (particularly ponatinib), and several prospective studies of these combinations are ongoing in both the frontline and relapsed/refractory settings.[57,76]

Highly effective combination approaches may decrease the need for HSCT in first remission for some patients, particularly if such regimens are capable of achieving higher rates of MRD negativity than traditional cytotoxic chemotherapy regimens.[77,78] To what extent these regimens may also decrease the need for HSCT in patients with high-risk pretreatment characteristics (e.g. adverse-risk cytogenetics, Ph-like ALL) remains to be determined. A particularly provocative question is whether HSCT is still required for many patients with relapsed/refractory disease treated with highly active monoclonal antibody combinations (e.g. mini-hyper-CVD + INO + blinatumomab). The outcomes of these combinations, particularly in first salvage, are promising, with a 2-year OS rate of 52% in those patients who did not undergo subsequent HSCT.[79] Longer follow up is needed to fully evaluate the role of HSCT in this setting.

Another open question is what the appropriate role of HSCT is for patients who have persistent or recurrent MRD after initial treatment but who convert to MRD negativity with blinatumomab treatment. Initial data suggest no survival benefit for HSCT in this setting[13]; however larger studies are needed to determine whether

foregoing HSCT in patients who achieved MRD negativity after blinatumomab is a reasonable and safe practice. An added uncertainty is whether monoclonal antibodies could be used for the treatment of MRD after HSCT over standard therapies that enhance the graft-*versus*-leukemia effect such as donor lymphocyte infusions (DLIs), natural killer cell infusions, or immunosuppression reduction.[80] To this end, blinatumomab is currently being investigated as post-HSCT remission maintenance for high-risk patients (ClinicalTrials.gov identifiers: NCT03114865 and NCT02807883), including in combination with DLI (ClinicalTrials.gov identifier: NCT03751709).

With the recent development and approval of chimeric antigen receptor (CAR) T-cell therapies for hematological malignancies, including ALL, there is uncertainty as to the proper sequencing of these agents. The anti-CD19 CAR T-cell product tisagenlecleucel is the first approved CAR T-cell therapy approved for relapsed/refractory ALL in children and young adults, with an ORR of over 80% and 5-year EFS and OS rates of 50% and 76%, respectively.[81] To date, the effect of prior blinatumomab exposure in patients undergoing CD19 CAR T-cell therapy is not fully known. There are concerns about blinatumomab-induced loss and disruption of CD19 membrane export.[82–84] However, remission with CAR T-cells after blinatumomab exposure is still possible.[85] In fact, theoretically additional leukemia debulking with blinatumomab (or other novel agents) prior to CAR T-cell therapy may increase the efficacy of CAR T-cells, while decreasing the risk of severe adverse events that are more common in patients higher disease burdens.

Finally, there is a particular unmet need for the development of active monoclonal antibody-based therapies for patients with T-cell ALL. The optimal target for this ALL subtype has yet to be determined, although several studies are ongoing exploring this important clinical question. Such novel therapies are particularly needed for the early T-cell precursor subtype, which is associated with poor outcomes with conventional therapy.[86]

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References

1. Terwilliger T and Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J* 2017; 7: e577.
2. Herold T, Schneider S, Metzeler K, *et al.* Philadelphia chromosome-like acute lymphoblastic leukemia in adults have frequent IGH-CRLF2 and JAK2 mutations, persistence of minimal residual disease and poor prognosis. *Haematologica* 2016; 102: 130–138, http://www.haematologica.org/cgi/doi/10.3324/haematol.2015.136366.
3. DeAngelo DJ, Stevenson KE, Dahlberg SE, *et al.* Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015; 29: 526–534.
4. Ecog U, Fielding AK, Richards SM, *et al.* Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12 / ECOG 2993 study. *Blood* 2012; 109: 944–950.
5. Kantarjian H, Thomas D, O'Brien S, *et al.* Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer* 2004; 101: 2788–2801.
6. Oriol A, Vives S, Hernández-Rivas J-M, *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: 589–596.

7. Jabbour E, O'Brien S, Ravandi F, *et al*. Monoclonal antibodies in acute lymphoblastic leukemia. *Blood* 2015; 125: 4010–4016.
8. Zhang X, Yang Y, Fan D, *et al*. The development of bispecific antibodies and their applications in tumor immune escape. *Exp Hematol Oncol* 2017; 6: 12.
9. Maury S, Chevret S, Thomas X, *et al*. Rituximab in B-Lineage adult acute lymphoblastic leukemia. *N Engl J Med* 2016; 375: 1044–1053.
10. 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: 3880–3889.
11. Maury S, Chevret S, Thomas X, *et al*. Addition of rituximab improves the outcome of adult patients with CD20-positive, Ph-negative, B-cell precursor acute lymphoblastic leukemia (BCP-ALL): results of the randomized graall-R 2005 study. *Blood* 2015; 126: 1, http://www.bloodjournal.org/content/126/23/1.abstract.
12. Kantarjian HM, DeAngelo DJ, Stelljes M, *et al*. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016; 375: 740–753.
13. 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: 1522–1531.
14. 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: 6330–6337.
15. Raponi S, Stefania De, Propris M, 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: 1098–1107.
16. 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: 1569–1580.
17. Ribrag V, Koscielny S, Bosq J, *et al*. Rituximab and dose-dense chemotherapy for adults with Burkitt's lymphoma: a randomised, controlled, open-label, phase 3 trial. *Lancet* 2016; 387: 2402–2411.
18. 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: 324–328.
19. Hoelzer D, Huettmann A, Kaul F, *et al*. Immunochemotherapy with rituximab improves molecular CR rate and outcome in CD20+ B-lineage standard and high risk patients; results of 263 CD20+ patients studied prospectively in GMALL study 07/2003. *Blood* 2010; 116: 170, http://www.bloodjournal.org/content/116/21/170.abstract.
20. Teeling JL, Mackus WJM, Wiegman LJJM, *et al*. The biological activity of human CD20 monoclonal antibodies is linked to unique epitopes on CD20. *J Immunol* 2006; 177: 362–371.
21. Wei G, Wang J, Huang H, *et al*. Novel immunotherapies for adult patients with B-lineage acute lymphoblastic leukemia. *J Hematol Oncol* 2017; 10: 1–13.
22. Bazarbachi AH, Yilmaz M, Ravandi F, *et al*. A phase 2 study of hyper-CVAD plus ofatumumab as frontline therapy in CD20+ acute lymphoblastic leukemia (ALL): updated results. *J Clin Oncol* 2018; 36(Suppl.): 7041.
23. Maiti A, Kantarjian H, Ravandi F, *et al*. Frontline ofatumumab with hyper-CVAD in CD20+ acute lymphoblastic leukemia (ALL): updated results of a phase II trial. *Clin Lymphoma Myeloma Leuk* 2017; 17: S256–S257.
24. Runcie K, Budman DR, John V, *et al*. Bi-specific and tri-specific antibodies- the next big thing in solid tumor therapeutics. *Mol Med* 2018; 24: 50.
25. Viardot A and Bargou R. Bispecific antibodies in haematological malignancies. *Cancer Treat Rev* 2018; 65(April): 87–95.
26. Topp MS, Gökbuget N, Zugmaier G, *et al*. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *J Clin Oncol* 2014; 32: 4134–4140.
27. Zugmaier G, Gökbuget N, Klinger M, *et al*. Long-term survival and T-cell kinetics in relapsed/refractory ALL patients who achieved MRD response after blinatumomab treatment. *Blood* 2015; 126: 2578–2584.

28. Aboudalle I, Kantarjian HM, Short NJ, *et al.* Long term follow-up on phase 2 study on the efficacy and safety of blinatumomab in adult patients with relapsed refractory B-precursor acute lymphoblastic leukemia. *Blood* 2018; 132(Suppl. 1): 4017.

29. Topp MS, Gökbuget N, Stein AS, *et al.* Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2015; 16: 57–66.

30. Kantarjian H, Stein A, Gökbuget N, *et al.* Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. *N Engl J Med* 2017; 376: 836–847.

31. Martinelli G, Boissel N, Chevallier P, *et al.* Complete hematologic and molecular response in adult patients with relapsed/refractory philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. *J Clin Oncol* 2017; 35: 1795–1802.

32. Cortes JE, Kim DW, Pinilla-Ibarz J, *et al.* Ponatinib efficacy and safety in Philadelphia chromosome–positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood* 2018; 132: 393–404.

33. United States Food and Drug Administration. FDA approves BLINCYTO™ (blinatumomab) immunotherapy for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia, http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-newsArticle&ID=1994704 (2014, accessed 13 January 2019).

34. United States Food and Drug Administration. FDA grants regular approval to blinatumomab and expands indication to include Philadelphia chromosome positive B cell. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566708.htm (11 July 2017). (accessed 31 December 2018).

35. Topp MS, Kufer P, Gökbuget N, *et al.* Targeted therapy with the T-cell - Engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol* 2011; 29: 2493–2498.

36. Topp MS, Gökbuget N, Zugmaier G, *et al.* Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. *Blood* 2012; 120: 5185–5187.

37. Goekbuget N, Dombret H, Zugmaier G, *et al.* Blinatumomab for minimal residual disease (MRD) in adults with B-cell precursor acute lymphoblastic leukemia (BCP-ALL): median overall survival (OS) is not reached in complete MRD responders at a median follow-up of 53.1 Months. *Blood* 2018; 132(Suppl. 1): 554.

38. United States Food and Drug Administration. FDA expands approval of Blincyto for treatment of a type of leukemia in patients who have a certain risk factor for relapse, https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm603151.htm (2018, accessed 13 January 2019).

39. Short NJ, Jabbour E, Albitar M, *et al.* Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: a consensus of North American experts. *Am J Hematol* 2019; 94: 257–265.

40. Kantarjian H, Thomas D, Jorgensen J, *et al.* Inotuzumab ozogamicin, an anti-CD22-calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol* 2012; 13: 403–411.

41. Al-Salama ZT. Inotuzumab ozogamicin: a review in relapsed/refractory B-cell acute lymphoblastic leukaemia. *Target Oncol* 2018; 13: 525–532.

42. Kantarjian H, Thomas D, Jorgensen J, *et al.* Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. *Cancer* 2013; 119: 2728–2736.

43. DeAngelo DJ, Stock W, Stein AS, *et al.* Inotuzumab ozogamicin in adults with relapsed or refractory CD22-positive acute lymphoblastic leukemia: a phase 1/2 study. *Blood Adv* 2017; 1:1167–1180.

44. United States Food and Drug Administration. FDA approves inotuzumab ozogamicin for relapsed or refractory B-cell precursor ALL, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm572133.htm (2017, accessed 31 December 2018).

45. Jabbour E, Short NJ, Jorgensen JL, *et al.* Differential impact of minimal residual disease negativity according to the salvage status in patients with relapsed/refractory B-cell acute lymphoblastic leukemia. *Cancer* 2017; 123: 294–302.

46. Sasaki K, Kantarjian HM, Ravandi F, *et al.* Sequential combination of low-intensity

chemotherapy (Mini-hyper-CVD) plus inotuzumab ozogamicin with or without blinatumomab in patients with relapsed/refractory Philadelphia chromosome negative acute lymphoblastic leukemia (ALL): a phase 2 trial. *Blood* 2018; 132(Suppl. 1): 553.

47. Jabbour E, Sasaki K, Ravandi F, *et al.* Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome–negative acute lymphoblastic leukemia in first salvage. *Cancer* 2018; 124: 4044–4055.
48. Jain N, Cortes JE, Ravandi F, *et al.* Inotuzumab ozogamicin in combination with bosutinib for patients with relapsed or refractory Ph + ALL or CML in lymphoid blast phase. *Blood* 2017; 130(Suppl. 1): 143.
49. Advani AS, Moseley A, O'Dwyer KM, *et al.* Results of SWOG 1318: a phase 2 trial of blinatumomab followed by pomp (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) maintenance in elderly patients with newly diagnosed Philadelphia chromosome negative B-cell acute lymphoblastic leukemia. *Blood* 2018; 132(Suppl. 1): 33.
50. Richard-Carpentier G, Kantarjian HM, Short NJ, *et al.* A phase II study of the hyper-CVAD regimen in sequential combination with blinatumomab as frontline therapy for adults with B-cell acute lymphoblastic leukemia (B-ALL). *Blood* 2018;132(Suppl. 1): 32.
51. 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: 240–248.
52. Short NJ, Jabbour EJ, Ravandi F, *et al.* Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, for newly diagnosed older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: results from a phase II study. *Blood* 2018; 132(Suppl. 1): 36.
53. Sasaki K, Kantarjian HM, Short NJ, *et al.* Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-hyper-CVD) Vs. standard intensive chemotherapy (hyper-CVAD) as frontline therapy for older patients with Philadelphia chromosome negative acute lymphoblastic leukemia (ALL): a prop. *Blood* 2018; 132(Suppl. 1): 34.
54. Jabbour E, Ravandi F, Kebriaei P, *et al.* Salvage chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD for patients with relapsed or refractory philadelphia chromosome-negative acute lymphoblastic leukemia: a phase 2 clinical trial. *JAMA Oncol* 2018; 4: 230–234.
55. Short NJ, Kantarjian H, Jabbour E, *et al.* Novel therapies for older adults with acute lymphoblastic leukemia. *Curr Hematol Malig Rep* 2018; 13: 91–99.
56. Assi R, Kantarjian H, Short NJ, *et al.* Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. *Clin Lymphoma Myeloma Leuk* 2017; 17: 897–901.
57. Assi R, Kantarjian HM, Short NJ, *et al.* Safety and efficacy of blinatumomab in combination with a tyrosine kinase inhibitor for the treatment of relapsed Philadelphia chromosome-positive leukemia. *Blood* 2017; 130(Suppl. 1): 2598.
58. Short NJ, Kantarjian H, Jabbour E, *et al.* Which tyrosine kinase inhibitor should we use to treat Philadelphia chromosome-positive acute lymphoblastic leukemia? *Best Pract Res Clin Haematol* 2017; 30: 193–200.
59. Chevallier P, Eugene T, Robillard N, *et al.* 90Y-labelled anti-CD22 epratuzumab tetraxetan in adults with refractory or relapsed CD22-positive B-cell acute lymphoblastic leukaemia: a phase 1 dose-escalation study. *Lancet Haematol* 2015; 2: e108–e117.
60. Fathi AT, Borate U, DeAngelo DJ, *et al.* A phase 1 study of denintuzumab mafodotin (SGN-CD19A) in adults with relapsed or refractory B-lineage acute leukemia (B-ALL) and highly aggressive lymphoma. *Blood* 2015; 126: 1328.
61. Kantarjian HM, Lioure B, Kim SK, *et al.* A phase II study of coltuximab ravtansine (SAR3419) monotherapy in patients with relapsed or refractory acute lymphoblastic leukemia. *Clin Lymphoma Myeloma Leuk* 2016; 16: 139–145.
62. Advani AS, McDonough S, Coutre S, *et al.* SWOG S0910: a phase 2 trial of clofarabine/cytarabine/epratuzumab for relapsed/refractory acute lymphocytic leukaemia. *Br J Haematol* 2014; 165: 504–509.
63. Short NJ, Kantarjian H, Jabbour E, *et al.* A phase I study of moxetumomab pasudotox in adults with relapsed or refractory B-cell acute lymphoblastic leukaemia. *Br J Haematol* 2018; 182: 442–444.

64. Jain N, Klisovic RB, Stock W, *et al*. Interim data from a phase 1 study evaluating pyrrolobenzodiazepine-based antibody drug conjugate ADCT-402 (loncastuximab tesirine) targeting CD19 for relapsed or refractory B-cell acute lymphoblastic leukemia. *Blood* 2017; 130(Suppl. 1): 1321.

65. Bride KL, Vincent TL, Im SY, *et al*. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. *Blood* 2018; 131: 995–999.

66. Bonda A, Punatar S, Gokarn A, *et al*. Daratumumab at the frontiers of post-transplant refractory T-acute lymphoblastic leukemia—a worthwhile strategy? *Bone Marrow Transplant* 2018; 53: 1487–1489.

67. Ganzel C, Kharit M, Duksin C, *et al*. Daratumumab for relapsed/refractory Philadelphia-positive acute lymphoblastic leukemia. *Haematologica* 2018; 103: e489–e490.

68. Ofran Y, Ganzel C, Harlev S, *et al*. Daratumumab in combination with vincristine or nelarabine as effective salvage therapy for patients with acute lymphoblastic leukemia at high risk of relapse. *Blood* 2018; 132(Suppl. 1): 5206.

69. Ravandi F, Bashey A, Foran JM, *et al*. Complete responses in relapsed/refractory acute myeloid leukemia (AML) patients on a weekly dosing schedule of XmAb14045, a CD123 x CD3 T cell-engaging bispecific antibody: initial results of a phase 1 study. *Blood* 2018; 132(Suppl. 1): 763.

70. Goldberg AD, Tallman MS, Solh MM, *et al*. Results from an ongoing phase 1 study indicate ACDT-301 (camidanlumab tesirine) is well-tolerated in patients with relapsed or refractory CD25-positive acute leukemia. *Blood* 2017; 130(Suppl. 1): 2662.

71. Hamadani M, Collins GP, Samaniego F, *et al*. Phase 1 study of Adct-301 (camidanlumab tesirine), a novel pyrrolobenzodiazepine-based antibody drug conjugate, in relapsed/refractory classical Hodgkin lymphoma. *Blood* 2018; 132(Suppl. 1): 928.

72. Duell J, Dittrich M, Bedke T, *et al*. Frequency of regulatory T cells determines the outcome of the T-cell-engaging antibody blinatumomab in patients with B-precursor ALL. *Leukemia* 2017; 31: 2181–2190.

73. Knaus H, Kanakry C, Luznik L, *et al*. Immunomodulatory drugs: immune checkpoint agents in acute leukemia. *Curr Drug Targets* 2017; 18: 315–331.

74. Webster J, Luskin MR, Prince GT, *et al*. Blinatumomab in combination with immune checkpoint inhibitors of PD-1 and CTLA-4 in adult patients with relapsed/refractory (R/R) CD19 positive B-cell acute lymphoblastic leukemia (ALL): preliminary results of a phase I study. *Blood* 2018; 132(Suppl. 1):557.

75. Jabbour E, Düll J, Yilmaz M, *et al*. Outcome of patients with relapsed/refractory acute lymphoblastic leukemia after blinatumomab failure: no change in the level of CD19 expression. *Am J Hematol* 2018; 93: 371–374.

76. King AC, Pappacena JJ, Tallman MS, *et al*. Blinatumomab administered concurrently with oral tyrosine kinase inhibitor therapy is a well-tolerated consolidation strategy and eradicates measurable residual disease in adults with Philadelphia chromosome positive acute lymphoblastic leukemia. *Leuk Res* 2019; 79: 27–33.

77. Berry DA, Zhou S, Higley H, *et al*. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: a meta-analysis. *JAMA Oncol* 2017; 3: 1–9.

78. Short NJ, Jabbour E, Sasaki K, *et al*. Impact of complete molecular response on survival in patients with Philadelphia chromosome–positive acute lymphoblastic leukemia. *Blood* 2016; 128: 504–507.

79. Jabbour E, Sasaki K, Ravandi F, *et al*. Chemoimmunotherapy with inotuzumab ozogamicin combined with mini-hyper-CVD, with or without blinatumomab, is highly effective in patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first salvage. *Cancer* 2018; 124(20): 4044–4055.

80. Rein LA, Sung AD and Rizzieri DA. New approaches to manipulate minimal residual disease after allogeneic stem cell transplantation. *Int J Hematol Oncol* 2013; 2(1): 39–48.

81. United States Food and Drug Administration. FDA approves tisagenlecleucel for adults with relapsed or refractory large B-cell lymphoma, https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm606540.htm (2018, accessed 16 March 2019).

82. Slaney CY, Wang P, Darcy PK, *et al*. CARs versus biTEs: a comparison between T cell–redirection strategies for cancer treatment. *Cancer Discov* 2018; 8: 924–934.

83. 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* 2016; 129: 100–104.

84. Ruella M and Maus MV. Catch me if you can: leukemia escape after CD19-directed T cell immunotherapies. *Comput Struct Biotechnol J* 2016; 14: 357–362.

85. Maude SL, Frey N, Shaw PA, *et al*. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med* 2014; 371: 1507–1517.

86. Jain N, Lamb AV, O'Brien S, *et al*. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood* 2016; 127: 1863–1869.