Naked antibodies and antibody-drug conjugates: targeted therapy for childhood acute lymphoblastic leukemia

Erica Brivio,[1] Francisco Bautista[1] and C. Michel Zwaan[1,2]

[1]Princess Máxima Center for Pediatric Oncology, Utrecht and [2]Pediatric Oncology, Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands

Correspondence: C.M. Zwaan
c.m.zwaan@prinsesmaximacentrum.nl

Received: November 8, 2023.
Accepted: March 15, 2024.

https://doi.org/10.3324/haematol.2023.283815

Abstract

The treatment of childhood acute lymphoblastic leukemia (ALL) has reached overall survival rates exceeding 90%. The present and future challenges are to cure the remainder of patients still dying from disease, and to reduce morbidity and mortality in those who can be cured with standard-of-care chemotherapy by replacing toxic chemotherapy elements while retaining cure rates. With the novel therapeutic options introduced in the last years, including immunotherapies and targeted antibodies, the treatment of ALL is undergoing major changes. For B-cell precursor ALL, blinatumomab, an anti-CD19 bispecific antibody, has established its role in the consolidation treatment for both high- and standard-risk first relapse of ALL, in the presence of bone marrow involvement, and may also have an impact on the outcome of high-risk subsets such as infant ALL and Philadelphia chromosome-positive ALL. Inotuzumab ozogamicin, an anti-CD22 drug conjugated antibody, has demonstrated high efficacy in inducing complete remission in relapsed ALL, even in the presence of high tumor burden, but randomized phase III trials are still ongoing. For T-ALL the role of CD38-directed treatment, such as daratumumab, is gaining interest, but randomized data are needed to assess its specific benefit. These antibodies are currently being tested in patients with newly diagnosed ALL and may lead to major changes in the present paradigm of treatment of pediatric ALL. Unlike the past, lessons may be learned from innovations in adult ALL, in which more drastic changes are piloted that may need to be translated to pediatrics.

Introduction

Significant improvements in the outcome of children with acute lymphoblastic leukemia (ALL) have been made in the past decades, with current rates of overall survival now exceeding 90%.[1] These results have been reached with the use of very intensive chemotherapeutic regimens, which are associated with acute toxicity as well as long-term side effects.[2] New therapeutic approaches are needed not only to cure the patients who currently still relapse and die from disease, but also to replace toxic therapy elements to mitigate treatment intensity and side-effects in those who can be cured with current chemotherapy, while maintaining cure rates.

With the novel therapeutic options introduced in the last years, including immunotherapies and targeted antibodies, ALL treatment is undergoing major changes. Treatment options for patients with B-cell precursor ALL (BCP-ALL) have increased significantly with the marketing authorization of blinatumomab and chimeric antigen receptor T cells (CAR T cells), changing the landscape for relapsed BCP-ALL.[3,4] For T-cell ALL, despite current high survival rates in first complete remission, first-relapse salvage rates remain dismal and there is no unified approach to relapse.[5] Nevertheless new approaches for relapsed T-ALL are also becoming available.[6,7] Among the novel therapeutic options, in this review we focus on the role of targeted antibodies, which have proven to be particularly effective for specific groups of pediatric ALL.

Targeted antibodies are designed with different mechanisms of action (Figure 1). Monoclonal antibodies, after binding a surface antigen, induce lysis through different cytotoxic mechanisms, including complement-dependent, cell-mediated and antibody-dependent cellular phagocytosis. Bispecific antibodies bind two distinct antigens simultaneously, linking antigens on target cells to immune effector cells (i.e.,

T cells, natural killer cells, or macrophages). Antibody-drug conjugates combine the targeting capabilities of monoclonal antibodies with cancer-killing abilities of cytotoxic drugs: once the monoclonal antibody-drug conjugates to the tumor antigen, the antigen-antibody complex is internalized and the cytotoxic agent is delivered inside the targeted tumor cells, resulting in a significantly improved therapeutic index and less toxicity to the normal cell compartment.[8]

The characterization of suitable target antigens is essential to the further development of new targeted antibodies. An ideal antigen should be exclusively and highly expressed on malignant cells, to minimize on-target/off-tumor side effects and maximize anticancer activity; it should be highly expressed in the majority of patients with a disease or even by different cancers types and the ability of rapid internalization after binding an antibody is another desirable characteristic especially for antibody-drug conjugates.[9] Multiple surface antigens have been identified as (potential) treatment targets in ALL. CD19 is expressed on the vast majority of B-cell malignancies, including 80% of ALL. CD22 is uniquely expressed in B-lymphocytes and in virtually all BCP-ALL.[10] CD20 is highly expressed in mature B-lineage cells and in a variable degree (30-50%) of BCP-ALL blasts.[11] CD123 represents another potential target, expressed in different genetic subtypes of BCP-ALL patients, while it is absent in T-ALL.[12] CD38 is expressed in pediatric ALL, including T-ALL.[13] Other potential targets for T-ALL are being explored, mainly in the development of CAR T-cell therapies: CD5, CD7 which is expressed on T lymphoblasts but also on effector T cells, and CD1a which is a target for cortical T-ALL.[14]

In this review we aim to present the available antibodies for the treatment of childhood ALL, focusing on the evidence generated so far and the future perspective of the use of antibodies in the treatment of childhood ALL.

Methods

The website *https://clinicaltrials.gov* was scrutinized using the advanced search mode to identify clinical trials exploring relevant monoclonal antibodies addressed to patients with ALL. Thirteen searches were conducted. For all searches, the pre-defined term “acute lymphoblastic leukemia” was used in the “condition or disease” box. In addition to this term, each search contained one of the

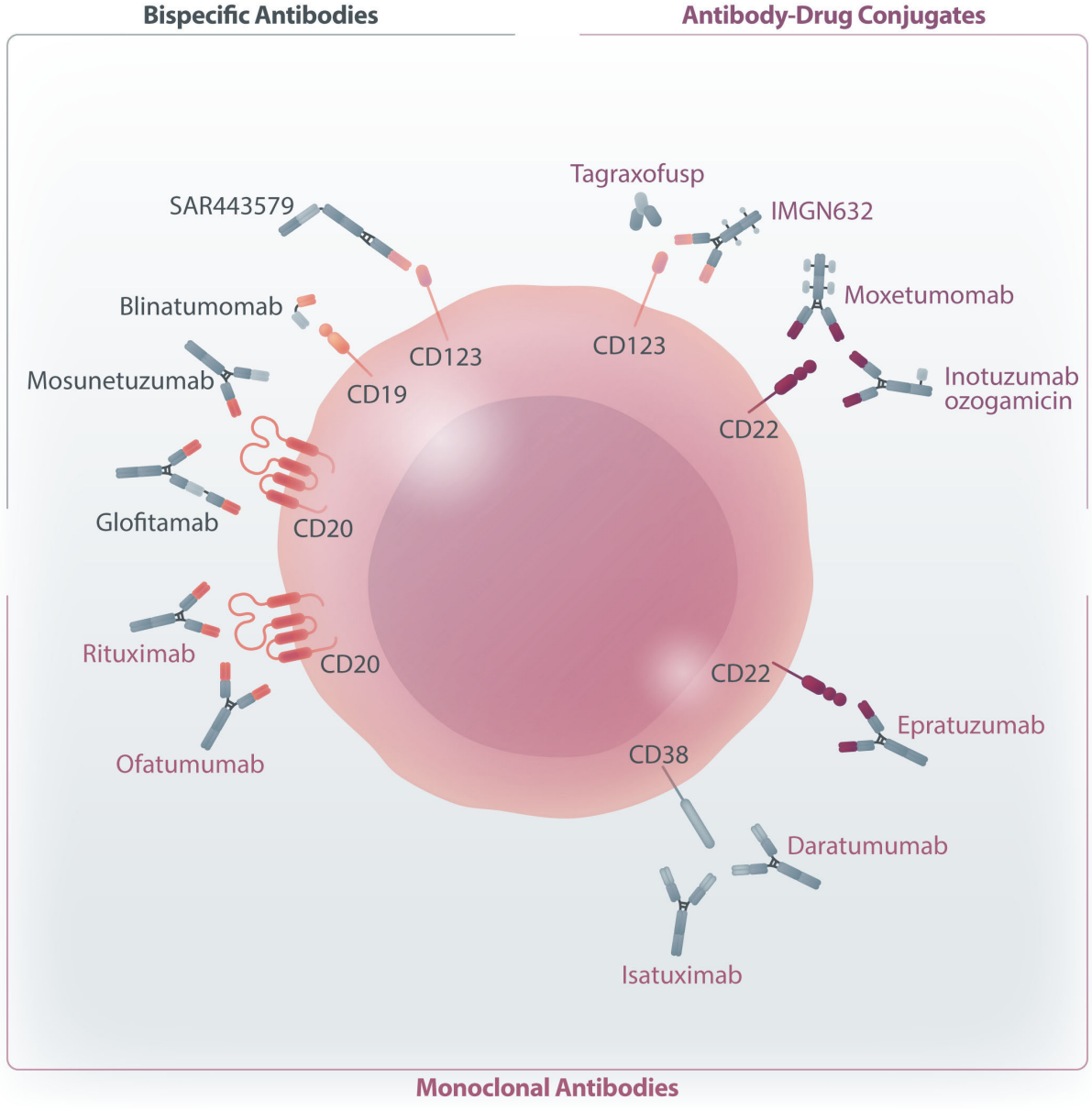

Figure 1. Targets and mechanism of actions of antibodies for pediatric acute lymphoblastic leukemia.

following pre-defined terms to identify relevant trials for the drugs covered in this review: "inotuzumab ozogamicin", "blinatumomab", "isatuximab", "daratumumab", "moxetumomab", "epratuzumab", "ofatumumab", "rituximab", "mosunetuzumab", "glofitamab", "tagraxofusp", "SAR443579", "IMGN632". Eligibility criteria were defined *a priori*: only interventional clinical trials in children were searched in the period from January 1, 2000 to August 1, 2023 and studies with unknown status were excluded.

The search was performed on August 28, 2023. In the results, we discuss the trials performed in children with ALL for which results have already been published (Table 1) or that are currently ongoing (Table 2).

Results

The search strategy at clinicaltrials.gov yielded 119 studies (*Online Supplementary Figure S1*, *Online Supplementary Table S1*). Of those, 84 fulfilled the eligibility criteria. Two studies were identified through cross-references.[15,16]

Anti-CD19: blinatumomab

Blinatumomab is a bispecific antibody that directs CD3-positive effector T cells to CD19-positive target cells. Blinatumomab is currently approved by the Food and Drug Administration as monotherapy for the treatment of children with relapsed or refractory (R/R) BCP-ALL, or in first or second complete remission with persisting positive minimal residual disease (MRD). In Europe, blinatumomab is indicated for patients above the age of 1 year, with second or beyond R/R BCP-ALL, or with high-risk first relapse BCP-ALL as part of consolidation therapy.

A phase I/II study of blinatumomab as a single agent in children with R/R B-BCP and bone marrow blasts ≥25% identified the stepwise dosage of 5/15 μg/m^2/day for further evaluation. The overall response rate at the recommended phase II dose was 39%, with 52% of those patients being MRD-negative.[3] This single-agent trial identified neurological toxicity (experienced by 24% of patients) and cytokine release syndrome (11% of patients) as blinatumomab-specific toxicities, the latter as a result of high tumor burden.[3] The RIALTO (NCT02187354) trial tested blinatumomab in the same R/R population, also allowing patients with persisting or re-emerging MRD ≥0.1% to be included, and documented a similar rate of MRD-negative complete remissions and low incidences of grade 3/4 cytokine release syndrome and neurological toxicity (1.8% and 3.6%, respectively). This trial clearly showed the need for consolidation with hematopoietic stem cell transplantation (HSCT) after blinatumomab treatment reinduction (1-year overall survival with *vs*. without allogeneic HSCT after blinatumomab: 87% *vs*. 29%, respectively).[17,18] After these initial experiences with blinatumomab in multiply R/R ALL, two randomized trials have highlighted the superiority (compared to chemotherapy) of one or two courses of blinatumomab monotherapy as post-reinduction consolidation treatment for first relapse ALL. This was due both to enhanced antileukemic activity as well as to lower toxicity than that with chemotherapy in the standard arm, especially inducing less hematologic toxicity and fewer infections. In the Children's Oncology Group (COG) phase III AALL1331 trial (NCT02101853) in intermediate- and high-risk first relapse of BCP-ALL, two cycles of blinatumomab as post-reinduction consolidation treatment produced a higher disease-free survival rate at 2 years compared to conventional chemotherapy (54.4% *vs*. 39.0%, respectively).[19] The NCT02393859 randomized trial demonstrated superior event-free survival for children with high-risk first relapse of BCP-ALL treated with blinatumomab as compared to those given a third block of consolidation chemotherapy before HSCT (2-year event-free survival: 66.2% *vs*. 27.1%, respectively).[20] More recently, blinatumomab has also been studied in standard-risk first relapse ALL in a randomized phase III trial in which blinatumomab was intercalated to continuation chemotherapy before maintenance, and tested against standard chemotherapy treatment. The 4-year disease-free and overall survival rates were superior for the blinatumomab group in the patients with bone marrow relapse (with or without extramedullary involvement), being 72.7% and 97.1% in the group treated with blinatumomab *versus* 53.7% and 84.8% in the group given chemotherapy. In contrast, for the patients with isolated extramedullary relapses, similar outcomes and poor disease-free survival were observed in both arms, with a 4-year disease-free survival rate of 36.6% for blinatumomab *versus* 38.8% for chemotherapy.[21] Based on these results, blinatumomab has become a new standard of care for post-induction consolidation therapy in high-risk first relapse ALL, and low-risk first relapse ALL in the case of bone marrow involvement. By contrast, unsatisfactory results were obtained in patients with isolated extramedullary relapse, possibly explained by the fact that blinatumomab does not cross the blood-brain barrier.

Overall, as in adults, blinatumomab seems to be more effective in circumstances of lower disease burden.[22] Importantly, in a study by Gokbuget *et al.,* although the MRD clearance rate was high also in patients with multiply relapsed ALL, these patients had substantially inferior relapse-free survival and overall survival compared with those treated in first remission.[22] This shows that the impact of clearance of MRD on survival is greatest when achieved early in the disease history.

Infants with ALL, carrying the *KMT2A* rearrangement in 80% of cases, have a poor prognosis, with a 4-year event-free survival rate of 47% and a survival rate after relapse of approximately 20%.[23,24] In this context of high medical need, a block of blinatumomab monotherapy was studied in newly diagnosed patients, as an addition to front-line chemotherapy. In a pilot study, one post-induction course of blinatumomab was added to the Interfant-06 back-

Table 1. Published results on targeted antibodies in pediatric acute lymphoblastic leukemia.

Study	Agent	Disease status	N	CR rate %	MRD negativity %	OS	EFS*	Ref
Blinatumomab								
NCT01471782	Blinatumomab	R/R BCP-ALL ≥2nd relapse; post-HSCT	70	39	55	Median: 7.5 months	-	3
RIALTO NCT02187354	Blinatumomab	R/R BCP-ALL ≥2nd relapse; post-HSCT	98	59	79	Median: 13.1 months	Median RFS: 8.5 months	17,18
NCT02393859	Blinatumomab	HR BCP-ALL 1st relapse	54	-	90	2-yr: 80%	2-yr: 66.2%	20
COG AALL1331 NCT02101853	Blinatumomab	IR or HR BCP-ALL 1st relapse	105	-	75	2-yr: 71.3%	2-yr: 54.4%	19
COG AALL1331 NCT02101853	Blinatumomab	SR BCP-ALL 1st relapse	255	-	-	4-yr: 90.4%	4-yr DFS: 61.2%	21
Blina Infant EudraCT2016-004674-17	Blinatumomab (added post-induction to Interfant-06 chemotherapy)	Newly diagnosed *KMT2A*-rearranged Infant BCP-ALL	30	-	93	2-yr: 93.3%	2-yr: 81.6%	25
NCT02807883	Post-HSCT prophylactic blinatumomab	HR for relapse after HSCT	21	-	-	1-yr: 85%	1-yr: 71%	35
Isatuximab								
ISAKIDS NCT03860844	Isatuximab + VXLD	R/R BCP-ALL/ T-ALL ≥1st relapse	17	41.2	-	-	-	83
Daratumumab								
NCT03384654	Daratumumab + VXLD	1st R/R T-ALL	24	83.3	41.7	-	-	6
Moxetumomab								
Phase I NCT00659425	Moxetumomab	R/R BCP-ALL ≥2nd relapse; post-HSCT	55	23	22	-	-	54
Phase II NCT02227108	Moxetumomab	BCP-ALL ≥1st relapse	32	10.7	-	-	-	55
Inotuzumab ozogamicin								
ITCC-059 Phase I	Inotuzumab	R/R BCP-ALL ≥2nd relapse; post-HSCT	27	80	84	1-yr: 40%	1-yr: 28%	16
ITCC-059 Phase II	Inotuzumab	R/R BCP-ALL ≥2nd relapse; post-HSCT	27	81.5	81.8	1-yr: 55%	1-yr: 36%	15
ITCC-059 Phase IB	InO + vincristine + dexamethasone	R/R BCP-ALL ≥2nd relapse; post-HSCT	30	76.7	65.2	1-yr: 58.1%	-	46
COG AALL1621	Inotuzumab	R/R BCP-ALL ≥2nd relapse; post-HSCT	48	58.3	66.7	2-yr: 36%	2-yr: 29%	41
INO-Ped-ALL-1	Inotuzumab	R/R BCP-ALL ≥1st relapse; post-HSCT	6	83.3	60	-	-	84

Continued on following page.

Study	Agent	Disease status	N	CR rate %	MRD negativity %	OS	EFS*	Ref
Epratuzumab								
COG Pilot Phase I	Epratuzumab + chemotherapy	BCP-ALL ≥1st relapse	15	60	77	-	-	52
COG ADVL04P2 Phase II	Epratuzumab + chemotherapy	HR BCP-ALL 1st relapse	54/60 (weekly/ bi-weekly epratuzumab)	65/66 (weekly/ bi-weekly epratuzumab)	31/39 (weekly/ bi-weekly epratuzumab)	2-yr: 34.2%/49.3% (weekly/ bi-weekly epratuzumab)	2-yr: 25.9%/ 39.9% (weekly/ bi-weekly epratuzumab)	53

*When disease-free survival or relapse-free survival is used, this is specified in the table. N: number; CR: complete remission; MRD: minimal residual disease; OS: overall survival; EFS: event-free survival; Ref: references; R/R: relapsed/refractory; BCP-ALL: B-cell precursor acute lymphoblastic leukemia; HSCT: hematopoietic stem cell transplantation; RFS: relapse-free survival; HR: high risk; yr: year; COG: Children's Oncology Group; IR: intermediate risk; SR: standard risk; DFS: disease-free survival; VXLD: vincristine, prednisone, pegylated asparaginase, and doxorubicin; InO: inotuzumab ozogamicin.

bone for infants with K*MT2A*-rearranged ALL. This addition provided a clear benefit to this group of patients, significantly increasing the rate of MRD negativity, with a 2-year disease-free survival of 81.6% in the study, as compared with 49.4% in the historical Interfant-06 trial, with corresponding overall survival values of 93.3% and 65.8%.[25] Despite the fact that these are non-randomized data, the effect size suggests that this should be a new standard of care also in infants with *KMT2A*-rearranged ALL, which will be confirmed prospectively in the Interfant-21 trial (NCT05327894). These excellent results and the promising findings with the menin-inhibitor revumenib may alter the poor prognosis of these patients in the near future.[26]

Currently, research is focused on moving blinatumomab to upfront treatment also in other groups of patients. The COG AALL1731 trial (NCT03914625), and the Berlin-Frankfurt-Münster (BFM)/Associazione Italiana Emato-Oncologia Pediatrica (AIEOP) (NCT03643276) trial include randomized questions of blinatumomab during consolidation. The ALLTogether1 trial (NCT03911128) evaluates blinatumomab as consolidation treatment in patients with Down syndrome, who have poor tolerance to chemotherapy. A warning about an increased risk of seizures during blinatumomab infusion in patients with Down syndrome >10 years old has been raised.[27] In clinical practice, blinatumomab has also been given to patients intolerant of chemotherapy during front-line treatment.[28] A retrospective study on 105 patients showed that the 2-year outcome of patients treated with blinatumomab as replacement for post-remission intensive chemotherapy was comparable to that of the chemotherapy-treated control group, with only one grade 3-4 adverse event occurring in the blinatumomab group.[29] In adults, the ECOG ACRIN E1910 randomized phase III trial showed that patients with newly diagnosed ALL who become MRD-negative (<0.01%) after induction chemotherapy have better survival when they are given four cycles of blinatumomab during consolidation chemotherapy than when they are given only chemotherapy. In contrast, a benefit could not be confirmed in patients who received only one or two cycles of blinatumomab.[30,31]

Novel strategies to overcome mechanisms of blinatumomab resistance are under investigation, including the combination with immune checkpoint inhibitors, such as nivolumab (COG trial AALL1821, NCT04546399).[32] Preclinical studies have shown increased PD-L1 expression on leukemic blasts in patients who are refractory to or relapse after blinatumomab treatment. Furthermore, *in vitro* studies suggest that the addition of PD-1 blockade to blinatumomab and ALL blasts leads to increased T-cell proliferation and enhanced blinatumomab-mediated cytotoxicity.[33]

Another area of interest is related to the use of this drug after HSCT to prevent relapse.[34] Blinatumomab seems a very good candidate for this use, considering its good tolerability, with low risk of infections and low rate of other toxicities such as liver toxicity, which prevents the use of many other drugs after a transplant. An MD Anderson trial, including pediatric patients, tested blinatumomab as a prophylactic treatment in patients at high risk of relapse after HSCT. The treatment was well tolerated, without requiring interruptions secondary to cytopenia. In this small cohort, the comparison to a matched control group did not demonstrate a clear clinical benefit, similar to what was observed in adults; nevertheless, it was highlighted that response to blinatumomab is dependent on the immune reconstitution following HSCT.[35] Other trials are using a pre-emptive approach, rather than prophylactic, treating patients with evidence of MRD positivity after HSCT (St. Jude trial NCT02790515). The FORUM consortium in Europe has designed a study with a dual approach, administering blinatumomab as a prophylactic treatment to patients undergoing HSCT with positive MRD and as a pre-emptive treatment for those becoming MRD-positive after the transplant (NCT04785547).

There are some data, mainly generated in adults, showing that prolonged blinatumomab administration may result in cure, and hence further studies also need to be performed to study the right schedule and duration of blinatumomab therapy and to determine its real potential to eradicate the disease without subsequent consolidation with HSCT.[22] Potential long-term side-effects will have to be considered

Table 2. Targeted antibodies in ongoing clinical trials in pediatric acute lymphoblastic leukemia.

Compound	Line of treatment	Phase	Age at enrollment	Trial number
Blinatumomab	Front-line ALL	III	≥1 year ≤31 years	COG ALL1731 NCT03914625
Blinatumomab	Front-line ALL	III	≤1 year	Interfant-21 NCT05327894
Blinatumomab	Front-line ALL	III	<18 years	AIEOP-BFM ALL 2017 NCT03643276
Blinatumomab	Front-line ALL	III	≤45 years	ALL together NCT03911128
Blinatumomab	Post-HSCT	II	≥6 months ≤21 years	FORUM NCT04785547
Blinatumomab	Post-HSCT (prophylactic)	II	≤21 years	St. Jude NCT02790515, NCT03849651
Blinatumomab + nivolumab	1st relapse ALL	III	≥1 year ≤31 years	COG AALL1821 NCT04546399
Daratumumab	T-ALL post-HSCT TBI-based conditioning	I	≤39 years	NCT04972942
Tagraxofusp	R/R ALL	I/II	≥1 year ≤21 years	NCT05476770
SAR443579	R/R ALL	I/II	≥1 year	NCT05086315
InO	1st relapse VHR ALL	II	≥1 year ≤18 years	ITCC-059 EudraCT 2016-000227-71
InO	1st relapse HR ALL	II with randomization	≥1 year <18 years	NCT05748171
InO	Front-line ALL	III	≥1 year ≤31 years	COG AALL1732 NCT03959085
InO	Front-line ALL	III	≤45 years	ALL Together NCT04307576
InO	Post-HSCT (prophylactic)	I/II	≥16 years	NCT03104491
InO	Post-HSCT (MRD positivity)	II	≥15 years	NCT05940961
InO	R/R MRD positive	II	≤21 years	St. Jude NCT03913559
InO + blinatumomab+ rituximab	R/R ALL	II	≥1 year ≤25 years	MD Anderson NCT05645718
InO + blinatumomab+ hyper-CVAD + rituximab or ofatumumab	Front-line ALL	II	≥14 years	MD Anderson NCT02877303
Rituximab or ofatumumab + CEC + liposomal vincristine + bortezomib	R/R ALL	II	≥14 years	MD Anderson NCT03136146

ALL: acute lymphoblastic leukemia; COG: Children's Oncology Group; AIEOP: Associazione Italiana Emato-Oncologia Pediatrica; BFM: Berlin-Frankfurt-Münster; HSCT: hematopoietic stem cell transplantation; TBI: total body irradiation; R/R: relapsed/refractory; InO: inotuzumab ozogamicin; VHR: very high risk, HR: high risk; MRD: minimal residual disease; CVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone; CEC: clofarabine, etoposide, cyclophosphamide.

in such trials as well. Indeed, decreased serum concentrations of immunoglobulins have been reported during and after treatment with blinatumomab (similarly to the changes after rituximab). Therefore, periodic monitoring of immunoglobulin levels may be considered in patients who are receiving or have received blinatumomab (as well as other antibodies against B cells) and IgG substitution treatment could be considered in patients experiencing severe infections.[36]

Anti-CD22

Inotuzumab ozogamicin

Inotuzumab ozogamicin (InO) is an anti-CD22 drug-conjugated antibody linked to calicheamicin, a potent cytotoxic agent, which causes cell death by inducing double-stranded DNA breaks.[37] *In vitro* studies demonstrated high efficacy of InO against BCP-ALL, related to the intrinsic high sensitivity of ALL blasts to calicheamicin, but also to the specific CD22 ligand-induced internalizing properties, which make repetitive loops of CD22 saturation, internalization and renewed CD22 expression not necessary to achieve intracellular threshold levels of calicheamicin sufficient for apoptosis.[38] Clinical data confirmed the high efficacy of InO in ALL, while failing to provide evidence of efficacy in non-Hodgkin lymphomas. The INO-VATE adult phase III study (NCT01564784), showed a complete remission rate of 80.7% in the InO arm as compared to 29.4% in the standard intensive chemotherapy control arm, and led to the approval of InO for adults with R/R CD22-positive BCP-ALL in 2017 by the Food and Drug Administration and European Medicines Agency.[39] The long-term follow-up also showed a benefit in survival with InO (2-year OS rates of 22.8% and 10.0%, respectively).

The first data on pediatric R/R BCP-ALL were collected from a compassionate use program, showing that InO as a single agent resulted in complete remissions in 67% of patients.[40] A phase I study in children with R/R BCP ALL

within the European Innovative Therapies for Children with Cancer Consortium (ITCC; the ITCC-059 trial) established that the recommended phase II dose of InO was 1.8 mg/m^2 fractionated in three dosages with an initial loading dose, as in adults, resulting in a high overall response rate of 80%. The phase II part of the study confirmed the very high response rate in the setting of multiple relapses and in patients relapsing after HSCT.[15,16] The COG phase II study, AALL1621, in the same subgroup of children and young adults with multiply R/R BCP-ALL, demonstrated an overall response rate of 58.6%.[41] It should be noted that none of these trials included children <1 year of age and experience with InO in infants is limited. Infant ALL, in the presence of a *KMT2A* rearrangement, is characterized by intrinsic resistance to chemotherapy, and by possibly lower CD22 expression, associated with immature leukemias arrested in the pro-B-cell stage.[10] A retrospective study showed a complete remission rate of 47% in R/R infant ALL (with a large majority of patients having a *KMT2A* rearrengement).[42] A particular concern with the use of InO is sinusoidal obstruction syndrome, likely due to the calicheamicin component. Warnings were raised by studies in adults, showing a high incidence in the transplant population (20% of transplanted patients following InO treatment).[43] The higher incidence of post-HSCT sinusoidal obstruction syndrome was confirmed in pediatric studies (26.1% in the ITCC-059 trial, 28.6% in the AALL1621 study).[16,41] In adult trials, conditioning regimens containing dual alkylators, high bilirubin levels and the number of treatment cycles received were identified as risk factors.[43] In the pediatric population, risk factors for developing post-HSCT sinusoidal obstruction syndrome are not yet supported by statistical evidence due to the limited sample size studied. The ITCC-059 trial identified a shorter time interval between the last InO dose and HSCT as the only significant risk factor.[15]

In adults, InO has already been studied in different combination strategies.[44,45] In the pediatric ITCC-059 trial, the combination of InO with a modified R3 reinduction regimen (5-day blocks of 20 mg/m^2 dexamethasone, weekly vincristine) showed comparable results to those in the single-agent part of the study, not providing evidence of further improvement with the addition of chemotherapy. Furthermore, liver toxicity was a limiting factor, requiring dexamethasone dose reduction (to 10 mg/m^2) and prohibiting the addition of asparaginase to the combination regimen. Nevertheless, heavily pretreated patients were included in this trial (after multiple relapses and/or after HSCT) and this might have had an impact on the added value of chemotherapy as well as the liver toxicity.[46] In the front-line setting, InO is also being studied in combination with chemotherapy, using a sequential model. The COG AALL1732 trial is testing InO in a phase III, randomized trial in newly diagnosed, high-risk, CD22-positive BCP-ALL (NCT03959085). Patients are randomized to chemotherapy or chemotherapy plus two cycles of InO after consolidation. After a first safety analysis showed increased rates of delayed methotrexate clearance following, and more sepsis events during, delayed intensifications in the arm including InO, the dose of this drug was reduced to 1.2 mg/m^2/cycle.[47] A later safety analysis raised concerns about the occurrence of sinusoidal obstruction syndrome during treatment, especially during thioguanine administration after InO, and so additional changes to the study are planned.[48] In the ALLTogether group, InO is being studied during consolidation for newly diagnosed ALL patients with persistent, high MRD (NCT04307576). In the front-line setting for adult ALL, the MD Anderson center is testing a different approach, with sequential use of hyperfractionated chemotherapy (hyper-CVAD) and lower-dose fractioned InO followed by blinatumomab (with or without CD20 targeted therapy with rituximab or ofatumumab), to shorten the duration of intensive chemotherapy, while improving safety and efficacy (NCT02877303, enrolling patients from 14 years of age).[49] Very high response rates are reported with such regimens, including in elderly ALL patients who cannot tolerate intensive chemotherapy.

Currently, the ITCC-059 trial is including a cohort of patients with very high-risk ALL in first relapse, defined as very early relapse within 18 months after the initial diagnosis and/or the presence of high-risk genetic features, who receive re-induction with single agent InO followed by consolidation with HSCT or CAR T cells once in complete remission. In a company-sponsored, randomized trial (NCT05748171) in patients with high-risk ALL in first relapse, defined in this case as relapse occurring within 18 to 30 months of the original diagnosis, and lacking any identified very high-risk genetic abnormalities, re-induction with InO monotherapy is being tested against ALL R3 block treatment (dexamethasone, vincristine, mitoxantrone, PEG-asparaginase). The plan is to further test InO against regular reinduction therapy also in standard-risk BCP-ALL in first relapse within the European IntReALL group.

An ongoing trial at St. Jude Children's Hospital is testing InO in R/R patients with persisting MRD positivity (NCT03913559) rather than as re-induction treatment. As with blinatumomab, a few trials including adolescents are testing the use of InO after HSCT, as prophylactic or pre-emptive treatment (NCT03104491, NCT05940961).

Mechanisms of resistance to InO still need to be fully understood. The ITCC-059 trial reported intrinsic resistance to calicheamicin, measured *ex-vivo* with a 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide (MTT)-based assay, broadly used to measure *in vitro* cytotoxic effects of drugs on cell lines, as the only factor related to the response.[15] Others reported low CD22 expression combined with high BCL-2 expression as a predictive factor for response to InO.[50] Potential synergistic mechanisms with BCL-2 inhibitors, such as venetoclax, as suggested by murine models, are being explored in adults (NCT05016947).[51]

Epratuzumab

Epratuzumab is a monoclonal antibody that binds CD22. A COG pilot study showed that epratuzumab in combination with standard reinduction chemotherapy was tolerable in children with first or later relapsed CD22-positive ALL, with a high rate of complete molecular remissions (47%).[52] Therefore, a phase II trial in early first relapse ALL was performed, but did not show improved rates of second complete remission compared to those in historical controls.[53] The European group InReALL tested epratuzumab in standard-risk ALL in first relapse in a randomized fashion against standard chemotherapy. Although the results of this trial have not yet been published, the randomization was prematurely suspended because of a stop in production of the drug.

Moxetumomab

Moxetumomab pasudotox, an anti-CD22 immunotoxin, failed to demonstrate significant activity in a phase II pediatric study,[54] preventing further investigation in children with ALL and the drug has been withdrawn from the US and European markets.[55]

Anti-CD20

Rituximab

Rituximab, a monoclonal antibody that binds to CD20, is currently the standard of care in addition to chemotherapy in mature B-cell non-Hodgkin lymphoma, and also as a single agent in post-transplant lymphoproliferative disease, especially in the case of Epstein-Barr virus-positive disease.[56] Its role in ALL is less well established, with only 30 to 50% of BCP-ALL blasts expressing CD20, including pediatric ALL.[11] CD20 expression has an adverse prognostic significance in adult ALL, while its impact in pediatric ALL is controversial.[57] A French trial in adults, in which rituximab was added to the ALL chemotherapy protocol, demonstrated an improved outcome for younger adults with CD20-positive, Philadelphia chromosome-negative ALL, and hence rituximab is now used in many adult treatment protocols.[58] The UKALL14 trial did not confirm the benefit of additional rituximab, but only four doses of rituximab were administered compared to 16–18 doses in the GRAAL trial.[59]

Novel anti-CD20 antibodies are being explored in the treatment of ALL, mainly for adult patients. These include ofatumumab, which targets a juxtamembrane, small-loop, extracellular epitope of CD20 and shows more potent *in vitro* complement-dependent cytotoxicity than rituximab. Research at MD Anderson showed that hyper-CVAD plus ofatumumab was associated with better outcomes than hyper-CVAD plus rituximab in newly diagnosed BCP-ALL. Although the trial was designed to include pediatric patients, only adults were enrolled.[60] Currently a study is open in MD Anderson for inclusion of patients from 14 years of age with R/R ALL (and Burkitt leukemia/lymphoma), testing CEC (cyclophosphamide, etoposide, clofarabine) and liposomal vincristine plus bortezomib and ofatumumab or rituximab (NCT03136146). Another study at MD Anderson is testing anti-CD20 antibodies in the Pedi-cRIB regimen (NCT05645718), which combines low-intensity chemotherapy with blinatumomab, InO and rituximab in a condensed regimen.

Other bispecific T-cell engagers such as glofitamab and mosunetuzumab, may be of interest for future studies in mature B-cell ALL or in non-Hodgkin lymphoma, as well as in CD20-positive BCP-ALL.[61] No studies open for pediatric patients were found in our search regarding these bispecific antibodies; nevertheless, they could gain a role for patients without other targets available (CD19, CD22), after multiple lines of therapy.

Anti-CD123

CD123 is widely expressed on a variety of hematologic malignancies, including some subtypes of BCP-ALL.[12] Multiple compounds targeting CD123 are currently in development. Tagraxofusp is a protein-drug conjugate consisting of human interleukin-3 fused to a truncated diphtheria toxin, approved as a single agent for the treatment of patients (from the age of 2 years in the USA) with blastic plasmacytoid dendritic cell neoplasm.[62] A Therapeutic Advances in Childhood Leukemia & Lymphoma (TACL) consortium phase I/II trial of tagraxofusp, as a single agent and in combination with chemotherapy, is enrolling pediatric patients with R/R hematologic malignancies, including ALL (NCT05476770). IMGN632 is another humanized anti-CD123 antibody linked to a novel DNA-alkylating payload of the indolinobenzodiazepine pseudodimer (IGN) class, approved by the Food and Drug Administration for the treatment of blastic plasmacytoid dendritic cell neoplasm.[63] Nevertheless, its development for pediatric leukemias has been discontinued (COG trial NCT05320380 withdrawn). SAR443579 is a natural killer-cell engager targeting CD123 that is currently being tested in a phase I/II trial open to children and adults with different hematologic malignancies, including ALL (NCT05086315).

Anti-CD38

Therapeutic CD38-targeting monoclonal antibodies (daratumumab, isatuximab; both G2 class antibodies), approved to treat adults with multiple myeloma, have been explored in pediatric ALL. Although CD38 expression in pediatric ALL might be lower than in multiple myeloma, promising preclinical data and the robust CD38 surface expression at diagnosis and relapse, especially in T-ALL, have led to the development of clinical trials.[13,64]

Daratumumab

Daratumumab is a monoclonal antibody that induces lysis through cytotoxic mechanisms (complement-dependent, cell-mediated and antibody-dependent cellular phagocytosis). It is approved as monotherapy and in combination with standard-of-care regimens for newly diagnosed and R/R multiple myeloma and in combination with standard-of-care regimens for systemic light chain amyloidosis. Daratumomab

has been evaluated in pediatric patients with R/R T-ALL and lymphoblastic lymphomas in a non-randomized phase I/II trial in combination with standard four-drug re-induction (vincristine, prednisone, PEG-asparaginase, and doxorubicin). Similar to other monoclonal antibodies, infusion reactions have been reported as the most common adverse event, for daratumomab as well as for isatuximab. Among T-ALL patients, 41.7% (n=10) achieved complete remission at the end of cycle 1, reaching the prespecified response rate.[6] However, these results are in the same range as, for example, the response rate of 33% (4/12) obtained in R/R T-ALL in the NECTAR trial (testing cyclophosphamide, etoposide, and nelarabine),[65] and hence a randomized trial is needed to establish the potential added benefit of treatment with daratumomab. A phase I trial open in the US is testing daratumumab monotherapy following a total body irradiation-based conditioning regimen and allogeneic HSCT in T-ALL (in patients aged 0-39 years) as prophylactic treatment to prevent post-transplant relapse (NCT04972942). Some reports in adults have described activity of daratumumab as a single agent in patients with T-ALL and molecular or morphological relapse.[66,67] There are also some reports of preclinical development of an antibody-drug conjugate targeting CD38, which could be of potential relevance for T-ALL in the future.[68]

A specific diagnostic challenge related to treatment with daratumomab is the long persistence of this antibody on the cell surface. Due to the fact that all diagnostic CD38 antibodies bind to epitopes overlapping with the daratumumab binding site, this may interfere with CD38 detection by flow cytometry for a long period (up to several months, as reported in multiple myeloma), especially in the context of MRD.[69] Moreover CD38 is expressed at low levels on red blood cells and daratumumab may mask the detection of antibodies in a patient's serum, interfering with the compatibility tests that are part of a routine pre-transfusion work-up.[70]

Isatuximab

Isatuximab is an immunoglobulin G1 class monoclonal antibody, also binding CD38, which exerts its activity by the same mechanisms as daratumumab.[71] The ISAKIDS study (NCT03860844) tested isatuximab in combination with chemotherapy for pediatric BCP/T-ALL and acute myeloid leukemia. A complete remission with or without complete hematologic recovery was observed in 13/25 (52.0%) patients in the B-ALL cohort, 5/11 (45.5%) in the T-ALL cohort, and 14/23 (60.9%) in the cohort with acute myeloid leukemia. These remission rates in individual cohorts did not meet the prespecified criteria to proceed to stage 2 of the ISAKIDS trial, which was therefore terminated.[72]

Perspectives

Targeted antibodies have already gained an established role in the treatment of pediatric ALL, mainly in the setting of relapsed BCP-ALL. Following the results of randomized trials, blinatumomab has established its role in consolidation treatment for both high- and standard-risk ALL with low tumor burden in first relapse, including cases with bone marrow involvement, while failing in the setting of standard-risk extramedullary relapse.[19-22] InO has demonstrated high efficacy in inducing MRD-negative complete remissions in relapsed ALL, even in the presence of high tumor burden, but randomized phase III trials are still ongoing.[15,16,41] In T-ALL, the role of daratumomab is gaining interest, but randomized data are still needed to really prove its benefit. CD20-directed therapy may be of use for patients who express this antigen, but has never been extensively investigated in children.

Novel targets are being explored to further expand the role of targeted therapy for ALL: CD47 is expressed on pediatric T-ALL blasts and blocking CD47 allows macrophages to phagocytose T-ALL blasts. Co-targeting CD47 and CD38 may have a synergistic effect, based on the fact that CD38 also plays a role in the regulation of phagocytosis.[73] CD79 is a B-cell-specific antigen expressed across the whole B-cell development. Antibody-drug conjugates targeting CD79 are in development for the treatment of lymphomas and could be potentially effective in BCP-ALL.[74] CD127 expression was found to high in T-ALL; the OSE-127 antibody, currently being evaluated in phase II trials in inflammatory and autoimmune diseases, is potentially attractive for the treatment of T-ALL.[75]

With multiple options of novel therapies (blinatumomab, InO, CAR T cells) available for R/R BCP-ALL, the best combination or sequence of treatment for a relapse or refractory state remains one of the most important unanswered questions at present. Some trials are already testing a combination of multiple antibodies, such as the multiagent regimen under investigation at MD Anderson, which combines low-intensity chemotherapy with blinatumomab, InO and rituximab in a condensed regimen (Pedi-cRIB regimen, NCT05645718).[76]

InO and/or blinatumomab are not considered stand-alone therapies and consolidation with an allogeneic HSCT or CAR T cells is recommended in the pediatric setting. Data regarding the safety profile of allogeneic HSCT after InO and blinatumomab are well known, with the important highlight of the risk of sinusoidal obstruction syndrome after HSCT following InO. Whether or not blinatumomab and InO are suitable bridging therapies before the administration of CAR T cells is the focus of more recent studies. Prior therapy with blinatumomab, directed to CD19 as the available CAR T-cell products, has been associated with higher rates of CAR T-cell failure.[51] Nevertheless, it was found that only patients with no response to blinatumomab had an inferior event-free survival after subsequent CAR T-cell therapy.[52] A possible effect of InO on CAR T-cell efficacy may be mediated by the reduction of CD19-positive

B cells, both leukemic and native, following InO treatment. It was previously reported that a bone marrow CD19-positive antigen load of less than 15% can be correlated with suboptimal expansion and persistence of CAR T cells.[53] However, a retrospective study showed similar response rates, overall survival and event-free survival for patients treated with InO prior to CAR T-cell therapy compared to published data regarding patients treated with CAR T cells without prior exposure to InO.[54]

The poorer outcome in the adult setting enables pilot trials of different strategies in larger populations with a dismal prognosis. An example is the combination of steroids, blinatumomab and tyrosine kinase inhibitors for induction in Philadelphia chromosome-positive ALL in adults, which opens the door to a possible 'chemo-free' reinduction.[77,78]

Innovations in the front-line setting for pediatric ALL have to compete with an overall survival rate of about 90% currently reached with the available, standard-of-care, poly-chemotherapy regimens.[79] InO and blinatumomab are now being introduced in front-line treatment for children with newly diagnosed ALL, as single agents given in treatment cycles during consolidation therapy (COG ALL1731, COG AALL1732, ALLTogether, AIEOP-BFM 2017). Although the introduction of novel agents in the front-line setting might be challenging because of the high overall survival rate reached with standard chemotherapy, the need to replace toxic elements is clear. Immunotherapy, antibodies and other targeted therapies (such as menin-inhibitors) will allow reductions in toxic deaths and morbidity rates from front-line treatment and improve the quality of life of survivors. Whether the current risk stratification of patients, based on historical survival data after chemotherapy treatment, would be the most appropriate one also for patients treated with regimens including novel agents will need to be verified. For example, InO is very effective in reinduction but a low level of MRD after InO monotherapy may not have the same implications as after four-drug induction. In addition, high-risk cytogenetics seem not to influence the outcome of newly diagnosed (adult) ALL patients treated with blinatumomab and/or InO.[80] Prognostic factors for response to antibody treatment are still largely unknown.[15,81]

Lastly, the very competitive arena and the commercial interests of manufacturers are critical in the process of selecting and prioritizing new agents for pediatric indications to avoid gaps and interruptions in the development of pediatric studies, highlighting the importance of collaborative efforts among stakeholders in order that childhood cancer drug development can prosper.[82]

Disclosures

CMZ has served as a consultant/advisory board member for Incyte, Takeda, Johnson & Johnson, Sanofi, Syndax, Agios, Bristol Meyers Squibb, Agios, Roche, Nektar Therapeutics, Kura Oncology Inc., Novartis, Pfizer, AbbVie, Daiichi Sankyo, Servier, and AstraZeneca; has sat on a steering committee for the Children's Oncology Group; has received study funds from Sanofi, Pfizer, and Novartis; and has received financial support for academic conferences and symposia from Allucent, Gilead, Kura Oncology, Novartis Pharma BV, Syndax, and Roche. EB and FB have no conflicts of interest to disclose.

Contributions

All authors conceived the review. EB and FB performed the literature search and revision. EB wrote the original draft. All authors were involved in writing, reviewing and editing the final manuscript.

References

1. Pieters R, Mullighan CG, Hunger SP. Advancing diagnostics and therapy to reach universal cure in childhood ALL. J Clin Oncol. 2023;41(36):5579-5591.
2. Sun W, Orgel E, Malvar J, et al. Treatment-related adverse events associated with a modified UK ALLR3 induction chemotherapy backbone for childhood relapsed/refractory acute lymphoblastic leukemia. Pediatr Blood Cancer. 2016;63(11):1943-1948.
3. von Stackelberg A, Locatelli F, Zugmaier G, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol. 2016;34(36):4381-4389.
4. 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.
5. Reismüller B, Attarbaschi A, Peters C, et al. Long-term outcome of initially homogenously treated and relapsed childhood acute lymphoblastic leukaemia in Austria – a population-based report of the Austrian Berlin-Frankfurt-Münster (BFM) study group. Br J Haematol. 2009;144(4):559-570.
6. Hogan LE, Bhatla T, Teachey DT, et al. Efficacy and safety of daratumumab (DARA) in pediatric and young adult patients (pts) with relapsed/refractory T-cell acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LL): results from the phase 2 DELPHINUS study. J Clin Oncol. 2022;40(16_suppl):10001.
7. Patel J, Gao X, Wang H. An update on clinical trials and potential therapeutic strategies in T-cell acute lymphoblastic leukemia. Int J Mol Sci. 2023;24(8):7201.
8. Attarwala H. Role of antibodies in cancer targeting. J Nat Sci Biol Med. 2010;1(1):53-56.
9. Bauer J, Nelde A, Bilich T, Walz JS. Antigen targets for the development of immunotherapies in leukemia. Int J Mol Sci. 2019;20(6):1397.
10. Shah NN, Stevenson MS, Yuan CM, et al. Characterization of CD22 expression in acute lymphoblastic leukemia. Pediatr Blood Cancer. 2015;62(6):964-969.
11. Dworzak MN, Schumich A, Printz D, et al. CD20 up-regulation in pediatric B-cell precursor acute lymphoblastic leukemia during induction treatment: setting the stage for anti-CD20 directed

immunotherapy. Blood. 2008;112(10):3982-3988.
12. Bras AE, de Haas V, van Stigt A, et al. CD123 expression levels in 846 acute leukemia patients based on standardized immunophenotyping. Cytometry B Clin Cytom. 2019;96(2):134-142.
13. Bras AE, Beishuizen A, Langerak AW, et al. CD38 expression in paediatric leukaemia and lymphoma: implications for antibody targeted therapy. Br J Haematol. 2018;180(2):292-296.
14. Cordo' V, van der Zwet JCG, Canté-Barrett K, Pieters R, Meijerink JPP. T-cell acute lymphoblastic leukemia: a roadmap to targeted therapies. Blood Cancer Discov. 2021;2(1):19-31.
15. Pennesi E, Michels N, Brivio E, et al. Inotuzumab ozogamicin as single agent in pediatric patients with relapsed and refractory acute lymphoblastic leukemia: results from a phase II trial. Leukemia. 2022;36(6):1516-1524.
16. Brivio E, Locatelli F, Lopez-Yurda M, et al. A phase I study of inotuzumab ozogamicin in pediatric relapsed/refractory acute lymphoblastic leukemia (ITCC-059 study). Blood. 2021;137(12):1582-1590.
17. Locatelli F, Zugmaier G, Mergen N, et al. Blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia: results of the RIALTO trial, an expanded access study. Blood Cancer J. 2020;10(7):77.
18. Locatelli F, Zugmaier G, Mergen N, et al. Blinatumomab in pediatric relapsed/refractory B-cell acute lymphoblastic leukemia: RIALTO expanded access study final analysis. Blood Adv. 2022;6(3):1004-1014.
19. Brown PA, Ji L, Xu X, et al. Effect of postreinduction therapy consolidation with blinatumomab vs chemotherapy on disease-free survival in children, adolescents, and young adults with first relapse of B-cell acute lymphoblastic leukemia: a randomized clinical trial. JAMA. 2021;325(9):833-842.
20. Locatelli F, Zugmaier G, Rizzari C, et al. Effect of blinatumomab vs chemotherapy on event-free survival among children with high-risk first-relapse B-cell acute lymphoblastic leukemia: a randomized clinical trial. JAMA. 2021;325(9):843-854.
21. Hogan LE, Brown PA, Ji L, et al. Children's Oncology Group AALL1331: phase III trial of blinatumomab in children, adolescents, and young adults with low-risk B-cell ALL in first relapse. J Clin Oncol. 2023;41(25):4118-4129.
22. 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.
23. Pieters R, De Lorenzo P, Ancliffe P, et al. Outcome of infants younger than 1 year with acute lymphoblastic leukemia treated with the Interfant-06 protocol: results from an international phase III randomized study. J Clin Oncol. 2019;37(25):2246-2256.
24. Tomizawa D, Koh K, Hirayama M, et al. Outcome of recurrent or refractory acute lymphoblastic leukemia in infants with MLL gene rearrangements: a report from the Japan Infant Leukemia Study Group. Pediatr Blood Cancer. 2009;52(7):808-813.
25. van der Sluis IM, de Lorenzo P, Kotecha RS, et al. Blinatumomab added to chemotherapy in infant lymphoblastic leukemia. N Engl J Med. 2023;388(17):1572-1581.
26. Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. Nature. 2023;615(7954):920-924.
27. Li AM, Rabin KR, Kairalla J, et al. Blinatumomab associated seizure risk in patients with Down syndrome and B-lymphoblastic leukemia: an interim report from Children's Oncology Group (COG) study AALL1731. Blood. 2021;138(Suppl 1):2304.
28. Gupta S, Casey J, Lasky J. Case report: blinatumomab as upfront consolidation and maintenance therapy in a pediatric patient with high-risk B-cell acute lymphoblastic leukemia. Front Oncol. 2023;13:1246924.
29. Hodder A, Mishra AK, Enshaei A, et al. Blinatumomab for first-line treatment of children and young persons with B-ALL. J Clin Oncol. 2024;42(8):907-914.
30. Litzow MR, Sun Z, Paietta E, et al. Consolidation therapy with blinatumomab improves overall survival in newly diagnosed adult patients with B-lineage acute lymphoblastic leukemia in measurable residual disease negative remission: results from the ECOG-ACRIN E1910 randomized phase III National Cooperative Clinical Trials Network trial. Blood. 2022;140(Suppl 2):LBA-1.
31. Luger SM, Sun Z, Mattison RJ, et al. Assessment of outcomes of consolidation therapy by number of cycles of blinatumomab received in newly diagnosed measurable residual disease negative patients with B-lineage acute lymphoblastic leukemia: in the ECOG-ACRIN E1910 randomized phase III National Clinical Trials Network trial. Blood. 2023;142(Suppl 1):2877.
32. 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.
33. Feucht J, Kayser S, Gorodezki D, et al. T-cell responses against CD19+ pediatric acute lymphoblastic leukemia mediated by bispecific T-cell engager (BiTE) are regulated contrarily by PD-L1 and CD80/CD86 on leukemic blasts. Oncotarget. 2016;7(47):76902-76919.
34. Ilan U, Brivio E, Algeri M, et al. The development of new agents for post-hematopoietic stem cell transplantation non-infectious complications in children. J Clin Med. 2023;12(6):2149.
35. Gaballa MR, Banerjee P, Milton DR, et al. Blinatumomab maintenance after allogeneic hematopoietic cell transplantation for B-lineage acute lymphoblastic leukemia. Blood. 2022;139(12):1908-1919.
36. Zugmaier G, Topp MS, Alekar S, et al. Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive B-precursor acute lymphoblastic leukemia. Blood Cancer J. 2014;4(9):244.
37. 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.
38. de Vries JF, Zwaan CM, De Bie M, et al. The novel calicheamicin-conjugated CD22 antibody inotuzumab ozogamicin (CMC-544) effectively kills primary pediatric acute lymphoblastic leukemia cells. Leukemia. 2012;26(2):255-264.
39. 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.
40. Bhojwani D, Sposto R, Shah NN, et al. Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Leukemia. 2019;33(4):884-892.
41. O'Brien MM, Ji L, Shah NN, et al. Phase II trial of inotuzumab ozogamicin in children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia: Children's Oncology Group protocol AALL1621. J Clin Oncol. 2022;40(9):956-967.

42. Brivio E, Chantrain CF, Gruber TA, et al. Inotuzumab ozogamicin in infants and young children with relapsed or refractory acute lymphoblastic leukaemia: a case series. Br J Haematol. 2021;193(6):1172-1177.
43. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab ozogamicin versus standard of care in relapsed or refractory acute lymphoblastic leukemia: final report and long-term survival follow-up from the randomized, phase 3 INO-VATE study. Cancer. 2019;125(14):2474-2487.
44. 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(2):230-234.
45. Short N, 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 lymphoblastic leukemia: updated results from a phase II study. Blood. 2022;140(Suppl 1):8966-8968.
46. Pennesi E, Brivio E, Ammerlaan ACJ, et al. Inotuzumab ozogamicin (InO) combined with UKALL-R3 modified chemotherapy in pediatric patients with B-cell precursor CD22+ acute lymphoblastic leukemia (BCP-ALL) - results from the ITCC-059 phase 1B trial. Blood. 2022;140(Suppl 1):8976-8978.
47. McNeer JL, O'Brien MM, Rheingold SR, et al. A phase 3 randomized trial of inotuzumab ozogamicin for newly diagnosed high-risk B-ALL: safety phase results from Children's Oncology Group protocol AALL1732. Blood. 2021;138(Suppl 1):3398.
48. O'Brien MM, McNeer JL, Rheingold SR, et al. A phase 3 trial of inotuzumab ozogamicin for high-risk B-ALL: second safety phase results from Children's Oncology Group AALL1732. J Clin Oncol. 2023;41(16_suppl):10016.
49. Jabbour E, Short NJ, Jain N, et al. The evolution of acute lymphoblastic leukemia research and therapy at MD Anderson over four decades. J Hematol Oncol. 2023;16(1):22.
50. Wintering A, Ishiyama K, Tamaki S, et al. CD22low/Bcl-2high expression identifies poor response to inotuzumab ozogamicin in relapsed/refractory acute lymphoblastic leukemia. Blood Adv. 2023;7(2):251-255.
51. Kirchhoff H, Karsli U, Schoenherr C, et al. Venetoclax and dexamethasone synergize with inotuzumab ozogamicin–induced DNA damage signaling in B-lineage ALL. Blood. 2021;137(19):2657-2661.
52. Raetz EA, Cairo MS, Borowitz MJ, et al. Chemoimmunotherapy reinduction with epratuzumab in children with acute lymphoblastic leukemia in marrow relapse: a Children's Oncology Group pilot study. J Clin Oncol. 2008;26(22):3756-3762.
53. Raetz EA, Cairo MS, Borowitz MJ, et al. Re-induction chemoimmunotherapy with epratuzumab in relapsed acute lymphoblastic leukemia (ALL): phase II results from Children's Oncology Group (COG) study ADVL04P2. Pediatr Blood Cancer. 2015;62(7):1171-1175.
54. Wayne AS, Shah NN, Bhojwani D, et al. Phase 1 study of the anti-CD22 immunotoxin moxetumomab pasudotox for childhood acute lymphoblastic leukemia. Blood. 2017;130(14):1620-1627.
55. Shah NN, Bhojwani D, August K, et al. Results from an international phase 2 study of the anti-CD22 immunotoxin moxetumomab pasudotox in relapsed or refractory childhood B-lineage acute lymphoblastic leukemia. Pediatr Blood Cancer. 2020;67(5):e28112.
56. Minard-Colin V, Aupérin A, Pillon M, et al. Rituximab for high-risk, mature B-cell non-Hodgkin's lymphoma in children. N Engl J Med. 2020;382(23):2207-2219.
57. Jeha S, Behm F, Pei D, et al. Prognostic significance of CD20 expression in childhood B-cell precursor acute lymphoblastic leukemia. Blood. 2006;108(10):3302-3304.
58. Maury S, Chevret S, Thomas X, et al. Rituximab in B-lineage adult acute lymphoblastic leukemia. N Engl J Med. 2016;375(11):1044-1153.
59. 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.
60. 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.
61. Lussana F, Gritti G, Rambaldi A. Immunotherapy of acute lymphoblastic leukemia and lymphoma with T cell–redirected bispecific antibodies. J Clin Oncol. 2021;39(5):444-455.
62. Pemmaraju N, Lane AA, Sweet KL, et al. Tagraxofusp in blastic plasmacytoid dendritic-cell neoplasm. N Engl J Med. 2019;380(17):1628-1637.
63. Kovtun Y, Jones GE, Adams S, et al. A CD123-targeting antibody-drug conjugate, IMGN632, designed to eradicate AML while sparing normal bone marrow cells. Blood Adv. 2018;2(8):848-858.
64. Bride KL, Vincent TL, Im S-Y, et al. Preclinical efficacy of daratumumab in T-cell acute lymphoblastic leukemia. Blood. 2018;131(9):995-999.
65. Whitlock JA, Malvar J, Dalla-Pozza L, et al. Nelarabine, etoposide, and cyclophosphamide in relapsed pediatric T-acute lymphoblastic leukemia and T-lymphoblastic lymphoma (study T2008-002 NECTAR). Pediatr Blood Cancer. 2022;69(11):e29901.
66. Prejzner W, Piekoś O, Bełdzińska K, et al. The role of daratumumab in relapsed/refractory CD38 positive acute leukemias-case report on three cases with a literature review. Front Oncol. 2023;13:1228481.
67. Cerrano M, Bonifacio M, Olivi M, et al. Daratumumab with or without chemotherapy in relapsed and refractory acute lymphoblastic leukemia. A retrospective observational Campus ALL study. Haematologica. 2022;107(4):996-999.
68. Li L, Tong W, Lau M, et al. Preclinical development of an anti-CD38 antibody-drug conjugate for treatment of hematological malignancies. Blood. 2019;134(Suppl_1):5621.
69. Oberle A, Brandt A, Alawi M, et al. Long-term CD38 saturation by daratumumab interferes with diagnostic myeloma cell detection. Haematologica. 2017;102(9):e368-e370.
70. Lancman G, Arinsburg S, Jhang J, et al. Blood transfusion management for patients treated with anti-CD38 monoclonal antibodies. Front Immunol. 2018;9:2616.
71. Deckert J, Wetzel MC, Bartle LM, et al. SAR650984, a novel humanized CD38-targeting antibody, demonstrates potent antitumor activity in models of multiple myeloma and other CD38+ hematologic malignancies. Clin Cancer Res. 2014;20(17):4574-4583.
72. Baruchel A, Bertrand Y, Nysom K, et al. Isatuximab plus chemotherapy for pediatric relapsed/refractory acute lymphoblastic leukemia or acute myeloid leukemia (ISAKIDS):

interim efficacy analysis. Hemasphere. 2023;7(S3):e121813.
73. Müller K, Vogiatzi F, Winterberg D, et al. Combining daratumumab with CD47 blockade prolongs survival in preclinical models of pediatric T-ALL. Blood. 2022;140(1):45-57.
74. Ferreri AJM. Targeted therapies make room, anti-CD79b agents are coming. Lancet Oncol. 2019;20(7):898-900.
75. Baccelli I, Lenk L, Laqua A, et al. CD127 is expressed by acute lymphoblastic leukemias and is efficiently targeted by the IL7R-antagonist OSE-127 through macrophage-mediated antibody dependent phagocytosis. Cancer Res. 2023;83(7_Supplement):2957.
76. McCall D, Jabbour E, Roth M, Nunez C, Cuglievan B. Mini-hyper CVD + CRIB (condensed rituximab, inotuzumab ozogamicin, and blinatumomab) for refractory pediatric B-acute lymphoblastic leukemia. Pediatr Blood Cancer. 2023;70(1):e29939.
77. 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.
78. Jabbour E, Short NJ, Jain N, et al. Ponatinib and blinatumomab for Philadelphia chromosome-positive acute lymphoblastic leukaemia: a US, single-centre, single-arm, phase 2 trial. Lancet Haematol. 2023;10(1):e24-e34.
79. Pui CH, Yang JJ, Hunger SP, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. J Clin Oncol. 2015;33(27):2938-2948.
80. Senapati J, Jabbour E, Short NJ, et al. Impact of high-risk cytogenetics (HR-CTG) on the outcome of newly diagnosed adult patients with Philadelphia negative B-cell acute lymphoblastic leukemia (B-ALL) treated with frontline blinatumomab (Blina) and/or inotuzumab ozogamicin (Ino) containing HyperCVAD (HCVAD) therapy. Blood. 2023;142(Suppl 1):1500.
81. Schultz L, Gardner R. Mechanisms of and approaches to overcoming resistance to immunotherapy. Hematology Am Soc Hematol Educ Program. 2019;2019(1):226-232.
82. Pearson ADJ, Weiner SL, Adamson PC, et al. ACCELERATE - Five years accelerating cancer drug development for children and adolescents. Eur J Cancer. 2022;166:145-164.
83. Baruchel A, Abrahamsson J, Bertrand Y, et al. Isatuximab in combination with chemotherapy in pediatric patients with relapsed/refractory acute lymphoblastic leukemia or acute myeloid leukemia (ISAKIDS): interim analysis. Blood. 2021;138(Suppl 1):516.
84. Nakayama H, Ogawa C, Sekimizu M, et al. A phase I study of inotuzumab ozogamicin as a single agent in pediatric patients in Japan with relapsed/refractory CD22-positive acute lymphoblastic leukemia (INO-Ped-ALL-1). Int J Hematol. 2022;116(4):612-621.