Immunotherapy of Acute Lymphoblastic Leukemia and Lymphoma With T Cell–Redirected Bispecific Antibodies

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review articles

INTRODUCTION

The outcome of B-cell precursor acute lymphoblastic leukemia (ALL) is different in children and adults, with overall survival (OS) rates at 5 years ranging from 90% to 45%.[1,2] Significant needs also remain unmet in patients with B-cell non-Hodgkin lymphoma (NHL), with rates of refractory disease up to 20% according to histology in the rituximab era.[3-5] In both ALL and NHL, many patients fail not only front-line but also salvage treatments, including allogeneic hematopoietic stem cell transplantation (alloHSCT). The therapeutic scenario for these patients with relapsed/refractory (R/R) disease is evolving, and immunotherapy is at the forefront. It took many years to move from the first to the current generation of bispecific antibodies that are changing the therapeutic landscape of acute leukemias and lymphomas.[6,7] Today the ability to produce recombinant antibodies allows the generation of bispecific antibodies with defined pharmacological properties (Fig 1).[8] Herein, we have reviewed the clinical development of antibodies designed to redirect the cytotoxic potential of nonantigen-specific T cells on specific antigens, such as CD19 and CD20 expressed on the cell surface of precursor and mature B lymphocytes.

BLINATUMOMAB: THE FIRST BISPECIFIC T-CELL ENGAGER

Blinatumomab, the first bispecific T-cell engager (BiTE) among these revolutionary molecules,[9] is an antibody composed of two single-chain variable antibody fragments (scFy) connected by a flexible linker. It binds specifically to CD19 expressed by precursor and mature B lymphocytes and CD3 expressed on the surface of T cells.[9-12] This results in cytotoxic CD3+ T-cell engagement against CD19-expressing cells, bypassing the barrier physiologically represented by the unique, antigen-specific T-cell receptor and the major histocompatibility complex. CD19 antigen is widely expressed during normal B-cell ontogeny; therefore, it is the most reliable surface marker for B cells and a good target antigen in ALL, chronic lymphocytic leukemia, and NHL.[13,14] Blinatumomab has a molecular weight of 54 kDa and a half-life of approximately 2 hours. It is metabolized in the bloodstream by protein cleavage into amino acids without any renal or hepatic clearance.[15] Because of its short pharmacokinetics, a continuous intravenous infusion (CI) is required.[16,17] Preclinical studies showed that there is no target saturation and that one T cell could engage more CD19+ cells.[12]

BLINATUMOMAB FOR R/R ALL: FROM CLINICAL TRIALS TO REAL-WORLD EXPERIENCE

Phase II studies led to the identification of the appropriate dose in R/R adult ALL (Table 1). The current treatment schedule is based on a ramp-up with 9 μg daily the first week followed by 28 μg daily for 28 days each subsequent cycle. Major achievements of blinatumomab in phase II studies have been the high proportion of complete hematologic response (CR/CRh), ranging from 43% to 69%, and the minimal residual disease (MRD) negativity obtained in approximately 80% of responders. About 40% of remitters could proceed to alloHSCT, and patients in first relapse did apparently better compared with second relapse or after a previous alloHSCT.[18] The relapse-free survival (RFS) and OS ranged from 5-8 months and 6-10 months, respectively.[18,19] A comparative analysis of these results also suggested a benefit for blinatumomab compared with a historical cohort,[20] but the regular approval by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for R/R Philadelphia (Ph)-negative ALL came from a phase III trial, the TOWER trial (ClinicalTrials.gov identifier: NCT02013167). Compared with the salvage chemotherapy arm, blinatumomab-treated patients had a median OS of 7.7 months versus 4.4 months (P = .011), and OS resulted in favor of blinatumomab in each patient subgroup, such as age, prior salvage treatment, or prior alloHSCT. The CR rate was 34% versus 16% (P < .001), and event-free survival was 31% versus 12% at 6 months (P < .001). Among patients who achieved CR, 76% were MRD negative in the blinatumomab treatment group versus 48% in the chemotherapy group.[21] The main blinatumomab toxicities were the cytokine release syndrome (CRS), neurotoxicity, and hypogammaglobulinemia.

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CONTEXT

Key Objective

Will the use of T cell–redirected bispecific antibodies change the immunotherapy landscape of acute lymphoblastic leukemia and lymphoma?

Knowledge Generated

Blinatumomab, the first bispecific T-cell engager (BiTE), has been approved for relapsed/refractory acute lymphoblastic leukemia. It is more effective and better tolerated than conventional chemotherapy. It is the first antileukemic drug approved for the treatment of minimal residual disease, a new treatment paradigm in medical oncology. Blinatumomab and other BiTEs are currently evaluated also in relapse/refractory lymphomas. The preliminary results are promising, and BiTEs may become an alternative to chimeric antigen receptor T cells.

Relevance

The antineoplastic activity and the relative ease of use of BiTEs make them an attractive therapeutic option in front-line treatment. BiTEs could reduce the indication to allogeneic and autologous transplantation. At the same time, they could improve the transplantation outcome when given either as a prophylaxis or as a postrelapse treatment.

After the European approval for the treatment of R/R Ph-negative ALL, blinatumomab has been made available to patients via an expanded access program. To minimize blinatumomab-related toxicities, patients (60% relapsed and 40% refractory) were pretreated with debulking chemotherapy or dexamethasone. Complete response was achieved by 51% (85% of these patients with MRD response), and 41% proceeded to alloHSCT. At 24 months after blinatumomab initiation, the median estimate of OS was 40% (36% after censoring for alloHSCT). Overall, the results obtained in this real-life setting confirm those achieved by clinical trials.[22]

The efficacy of blinatumomab has also been evaluated in R/R Ph-positive ALL in a multicenter single-arm trial (ALCANTARA; ClinicalTrials.gov identifier: NCT02000427). CR/CRh was achieved by 36% of patients during the first two cycles, including some with the T315I mutation. Among responders, 88% of patients achieved a complete MRD response. Median RFS and OS were 6.7 and 7.1 months, and 44% of responders proceeded to alloHSCT.[23] A propensity score analysis was performed to compare outcomes of patients treated with blinatumomab in the ALCANTARA study with those of an external cohort of patients receiving standard chemotherapy. A higher rate of CR/CRh (36% v 25%) and better OS with a hazard ratio of 0.81 (95% CI, 0.57 to 1.14) was seen after blinatumomab.[24] The results in R/R Ph-positive patients are in keeping with those obtained in Ph-negative ALL. Although confirming the efficacy of blinatumomab in terms of hematologic and molecular response, the impact on duration of response remains less impressive.

These results have been confirmed in the pediatric setting. In a phase I/II dose-escalation/dose-expansion trial, blinatumomab was studied in patients with Ph-negative ALL, refractory or relapsed after at least two lines of therapy or alloHSCT. The pediatric recommended dose is 5 $\mu g/m^2/d$ for the first 7 days, then 15 $\mu g/m^2/d$.[25] Complete remission was achieved by 39% of the patients, with MRD negativity in 52% of responders. Median RFS and OS were 4.4 and 7.5 months, respectively. The long-term follow-up of this study at 24 months showed a survival of 20%, and there was no difference in OS between transplanted and nontransplanted responders.[26] When this study was compared with three historical comparator groups, single-agent blinatumomab treatment was associated with longer OS in comparison with standard chemotherapy.[27] The randomized, phase III AALL1331 trial (ClinicalTrials.gov identifier: NCT02101853), conducted by the Children's Oncology Group in patients < 30 years old, showed that blinatumomab is superior to standard chemotherapy as post-reinduction consolidation before alloHSCT, resulting in fewer and less-severe toxicities, higher rates of MRD response, greater likelihood of proceeding to alloHSCT, and improved RFS and OS.[28]

Blinatumomab proved effective even in some rare chemorefractory ALL subtypes, such as those bearing the t(17;19) and the related TCF3-HLF fusion gene, which is usually characterized by a high rate of treatment failure despite treatment intensification and alloHSCT.[29]

BLINATUMOMAB IS THE FIRST DRUG APPROVED FOR THE TREATMENT OF MRD

In both childhood and adult ALL, the persistence of MRD represents the most informative prognostic factor of poor outcome.[30] The early results obtained in the R/R setting showed the ability of blinatumomab to induce not only hematologic but also molecular remission.[18] For this reason, blinatumomab has also been extensively tested in patients with molecular evidence of MRD in first or later CR. In the first phase II pilot study conducted in 21
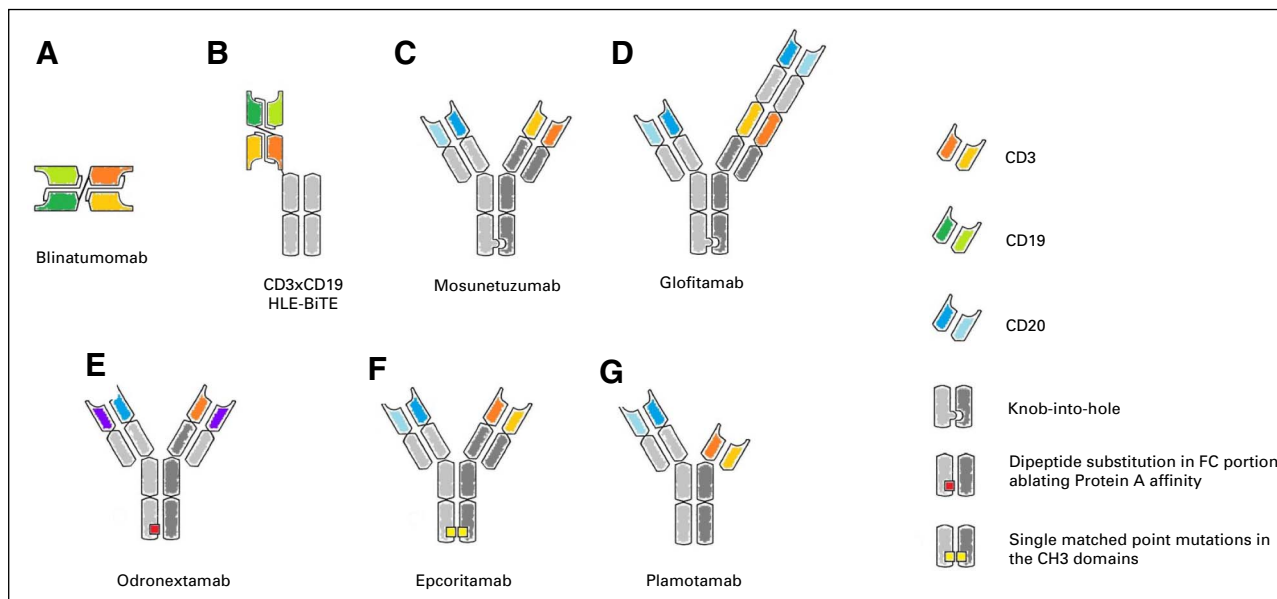
FIG 1. Main T cell–redirecting bispecific antibodies in clinical development. (A) Blinatumomab, the first bispecific T-cell engager (BiTE), is a tandem single-chain variable fragment (scFv). (B) To increase the half-life, the CD3xCD20 BiTE it is linked to a silent fragment crystallizable region (constant; FC) portion to form the half-life extended (HLE)-BiTE. (C, D) The knob-into-hole technology facilitates the correct pairing of FC portion of mosunetuzumab and glofitamab; this latter is characterized also by an asymmetric 2:1 format that incorporates bivalent binding to CD20 and monovalent binding to CD3 (CrossMAb). (E) Design of odronextamab exploits differences in the affinities of the immunoglobulin isotypes for Protein A coupled with the use of common light chain, allowing efficient large-scale purification. (F) In the Duo-Body, each parental antibody contains single matched point mutations in the constant region of the heavy chain 3 (CH3) domains, which allows the correct reassembly after in vitro separation (controlled fragment antigen-binding [Fab]-arm exchange). (G) Plamotamab uses FC domain variants that spontaneously form stable, heterodimeric bispecific antibodies allowing the use of standard antibody production methods. Different from the other molecules, the FC domain is functional.

MRD-positive patients, a major MRD response was achieved in 80% of patients after one cycle of treatment. Most notably, 10 out of 11 patients with a high MRD load ($\geq 10^{-2}$) achieved a molecular remission. The clinical outcome after achieving molecular remission was not different for patients having or not a subsequent alloHSCT. It is worth noting that a reduced transplant-related mortality was observed in this small cohort, suggesting that the sequence of inducing MRD response by blinatumomab followed by alloHSCT is safe. An RFS estimate of 61% at a median observation of 33 months was reported.[31,32] A subsequent larger, confirmatory multicenter phase II study of 116 patients was performed enrolling adults with ALL in hematologic CR with a high MRD level ($\geq 10^{-3}$). After one cycle of blinatumomab, the primary end point was achieved by 78% of patients.[33] In a long-term follow-up analysis, the median OS was 36.5 months, and it was not reached among patients who achieved a complete MRD response after the first cycle of blinatumomab.[34] On the basis of these results, in March 2018, the FDA granted the first approval to treat a patient in the MRD setting, confirmed on January 2019 by the EMA.

Before country-specific reimbursement, blinatumomab was made available to MRD-positive patients under an expanded access program. MRD assessment was undertaken as per local clinical practice, including flow cytometry and polymerase chain reaction. After blinatumomab, 68% proceeded to alloHSCT, being in CR in 88% of cases before transplantation. The median RFS was 27.6 months, and at 24 months the OS was 65%. These results confirmed that in a real-life setting, two cycles of blinatumomab are able to induce molecular response in the majority of patients.[35]

Blinatumomab proved effective when given alone or in combination with donor lymphocyte infusion to pediatric[36,37] and adult patients with ALL relapsed after alloHSCT.[38,39] Blinatumomab is also currently being investigated to prevent leukemia relapse post alloHSCT in high-risk patients for biologic characteristics (ClinicalTrials.gov identifier: NCT03114865), or MRD positivity (ClinicalTrials.gov identifier: NCT03982992), or both (ClinicalTrials.gov identifier: NCT02807883). On the same rationale, targeting leukemic blasts with BiTE against CD123 (ClinicalTrials.gov identifier: NCT02715011) and CD33 (ClinicalTrials.gov identifier: NCT02520427) is currently under investigation in the setting of acute myeloid leukemia,[40] where other posttransplant strategies are rapidly developing.[41]

WHAT TO DO IN SECOND REMISSION AFTER BLINATUMOMAB: alloHSCT OR MAINTENANCE?

In both phase II and TOWER studies, the option to proceed to alloHSCT was left free after two cycles of blinatumomab. However, the available results do not show a clear clinical

TABLE 1. Main Clinical Trials With Blinatumomab

Short Title, Study Design, and Reference	Treatment Schedule and No. of Patients	Hematologic Response (CR/CRh) (%)	Molecular Response (%)	Subsequent alloHSCT (%)	Median RFS (months)	Median OS (months)
MRD positive after induction/ consolidation; phase II study[31]	15 μg/m²/d CI (N = 20)	NA	80	40	78% at median follow-up of 405 days	NR
Hematologic and molecular remission in R/R BCP-ALL; phase II GMALL study[18]	5-30 μg/m²/d CI (N = 36)	69	88	36	7.6	9.8
Safety and activity in BCP-ALL phase II, international multicenter study[19]	9 μg/d first week, then 28 μg/d CI (N = 189)	43	82	17	5.9	6.1
Blinatumomab v chemotherapy for R/ R BCP-ALL; randomized international phase III study[21]	9 μg/d first week, then 28 μg/d CI (n = 271 blina v 134 CHT)	Blina 34 v CHT 16	Blina 76 v CHT 48	Blina 24 v CHT 24	Blina 7.3 v CHT 4.6	Blina 7.7 v CHT 4.0
MRD positive after induction phase II international study[33]	15 μg/m²/d CI (N = 113)	NA	78	67	18.9	36.5
Hematologic and molecular remission in R/R Ph+ ALL; phase II international study[23]	9 μg/d first week, 28 μg/ d CI (N = 45)	36	88	16	6.7	7.1
Pediatric R/R ALL, phase I-II[25]	5 μg/m²/d first week, 15 μg/m²/d CI thereafter (N = 70)	39	52	19	4.4	7.5

Abbreviations: ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; BCP-ALL, B cell precursor acute lymphoblastic leukemia; blina, blinatumomab; CHT, chemotherapy; CI, continuous infusion; CR, complete response; CRh, complete hematologic response; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; MRD, minimal residual disease; NA, not applicable; NR, not reported; OS, overall survival; Ph+, Philadelphia positive; R/R, relapsed refractory; RFS, relapse-free survival.

benefit for patients proceeding to transplantation.[19,21] In particular, the results of the TOWER study after censoring for alloHSCT did not show a significant increase in terms of OS. In addition, blinatumomab continuation therapy (≥ six cycles) and maintenance were associated with an increased OS and RFS compared with patients not receiving maintenance independently from consolidation with alloHSCT.[42] In patients treated for MRD positivity in first CR, the OS was not different in patients who did or did not undergo transplantation, whereas for those treated in second or later CR, the outcome of patients who did not undergo transplantation was inferior.[33] Nonetheless, in a long-term analysis of a phase II study conducted in the MRD setting, younger patients (≤ 35 years) who underwent alloHSCT had a better 3-year survival compared with those who did not (62% v 22%).[43] In the real-life setting, alloHSCT after blinatumomab salvage therapy has been confirmed as an effective postremission treatment, with RFS at 2 years of 40%.[44] No unexpected toxicities or increase rate of graft-versus-host disease grades II to IV were reported. At our institution, for patients < 55 years old, the alloHSCT remains the first option.

BLINATUMOMAB WITH CHEMOTHERAPY OR OTHER DRUGS IN FRONT-LINE TREATMENT

Several trials are currently evaluating blinatumomab as part of front-line treatment (Table 2; Fig 2). In this setting, blinatumomab is particularly attractive, because it is highly active in MRD-positive patients and well tolerated in patients undergoing alloHSCT, with no additional risk of venous occlusive disease or any other transplant-related toxicity.[44] Thus, it is expected that incorporation of this immunotherapy will lead to a significant improvement of the cure rate in adult patients with ALL. Two phase III studies in adult (ClinicalTrials.gov identifier: NCT02003222) and pediatric (ClinicalTrials.gov identifier: NCT03914625) ALL are currently ongoing, with blinatumomab randomly added to conventional chemotherapy with the aim to improve RFS. Several phase II studies have been launched by cooperative study groups (Table 2). The primary end point is to increase the rate and depth of MRD negativity as a powerful surrogate of more robust clinical end points, such as RFS and OS. In these studies, blinatumomab has been added at different points during treatment, ranging from prephase to consolidation or maintenance. The results of these studies will help to establish the correct positioning of blinatumomab in the future up-front therapeutic regimens.

The GIMEMA LAL2116 D-ALBA trial (ClinicalTrials.gov identifier: NCT02744768) evaluated a front-line chemotherapy-free regimen using the combination of dasatinib and blinatumomab for Ph-positive ALL. Dasatinib, 140 mg daily, was administered as induction for 85 days, followed by a postinduction consolidation with blinatumomab. At the end of the second cycle of blinatumomab, a molecular response was reported in 54% of patients,

TABLE 2. Ongoing Clinical Trials With Front-Line Blinatumomab in Pediatric and Adult ALL

Short Title	Primary End Points	Study Design, Sponsor, and NCT Identifier
Blinatumomab added to prephase and consolidation therapy in BCP-ALL	MRD negativity	Phase II, HOVON, NCT03541083
Blinatumomab in consolidation and maintenance in patients with high-risk BCP-ALL	Disease-free survival at 3 years	Phase II, GRAAL, NCT03709719
Combination chemotherapy with or without blinatumomab for newly diagnosed BCR-ABL–negative BCP-ALL	Overall survival	Phase III, ECOG, NCT02003222
Blinatumomab in sequential combination with hyper-CVAD as front-line therapy for BCP-ALL	Relapse-free survival at 2 years	Phase II, MDACC, NCT02877303
Blinatumomab with sequential dose-reduced chemotherapy in older patients with BCR-ABL–negative BCP-ALL	Hematologic and MRD response after induction therapy	Phase II, EWALL, NCT03480438
Blinatumomab during consolidation to reduce mrd in patients with high-risk BCP-ALL	Reduction of MRD determined by MFC	Phase II, PETHEMA, NCT03523429
Front-line sequential treatment with dasatinib and blinatumomab in ph+ BCP-ALL	MRD negativity	Phase II, GIMEMA, NCT02744768
Blinatumomab with sequential chemotherapy to improve MRD response and survival in BCR-ABL negative BCP-ALL	MRD negativity	Phase II, GIMEMA, NCT03367299
Blinatumomab in combination with chemotherapy in pediatric and AYA patients with BCP-ALL	Disease-free survival up to 5 years	Phase III, NCI-COG, NCT03914625
Blinatumomab in adult patients with MRD of BCP-ALL (blast successor trial)	MRD negativity after one cycle	Phase II, GMALL, NCT03109093
Combination of blinatumomab and ponatinib in Ph+ BCP-ALL	MRD negativity	Phase II, MDACC, NCT03263572

Abbreviations: AYA, adolescent and young adult; BCP-ALL, B cell precursor acute lymphoblastic leukemia; ECOG, Eastern Cooperative Oncology Group; EWALL, European Working Group on ALL; GIMEMA, Gruppo Italiano Malattie EMatologiche dell'Adulto; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; GRAAL, French Group for Research on Adult Acute Lymphoblastic Leukemia; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Group; Hyper-CVAD, hyperfractionated cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), and dexamethasone; MRD, minimal residual disease; MDACC, MD Anderson Cancer Center; MFC, multicolor flow cytometry; NCI-COG, National Cancer Institute–Children's Oncology Group; NCT, Clinical Trial Registry; Pethema, Programa para el Tratamiento de Hemopatías Malignas; Ph+, Philadelphia positive.

which further increased to 68% and 80% after the third and fourth cycles, respectively. The 12-month OS and RFS were 94% and 87%, respectively.[45] A phase II trial using blinatumomab and ponatinib combination in patients > 60 years with previously untreated Ph-positive ALL is currently ongoing (ClinicalTrials.gov identifier: NCT03263572). Another intriguing combination is the use of blinatumomab after treatment with inotuzumab ozogamicin. A phase II study has been launched by the National Cancer Institute in newly diagnosed older adults or adults with R/R ALL (ClinicalTrials.gov identifier: NCT03739814).

The results from these studies may lead to the development of innovative chemotherapy-free treatment modalities for patients with ALL.

BLINATUMOMAB FOR R/R B-CELL NHL

Patients with R/R NHL were the first in whom blinatumomab was tested as a salvage treatment.[9] In a phase I study, the maximum tolerated dose was identified as 60 μg/m^2/d given by CI for 6 weeks, and strategies to mitigate the toxicity were implemented. Among the 35 patients treated at the target dose, the overall response rate (ORR) was 69% (CR rate, 37%), with an excellent durability of response (median response, 404 days).[46] High response rates were observed in most lymphoma subtypes, including follicular (80%), mantle cell (71%), and diffuse large B-cell (DLBCL) lymphomas (55%). Despite the weekly dose escalation and preemptive dexamethasone treatment, neurotoxicity was the most relevant adverse event, occurring in 71% of the patients (22% grade 3, 0% grade 4-5). Although transient and without long-term effects, neurologic events represented the limiting toxicity.[46,47]

The encouraging ORR prompted further studies. In a phase II trial, 23 patients with DLBCL were treated with stepwise doses (9-28-112 μg/d, with weekly dose increases), with a target dose of 112 μg/d by CI for 8 weeks. The ORR among the 21 evaluable patients after one cycle was 36% (CR, 16%), and the exposure to at least 1 week of treatment at the target dose of 112 μg/d appeared to be required for efficacy. However, the need for 2 weeks of treatment at subtherapeutic doses (9-28 μg/d) limited the potential efficacy of the molecule in this setting of rapidly proliferating lymphomas, and a more aggressive dose escalation schedule was hampered by severe neurotoxicity.[48]
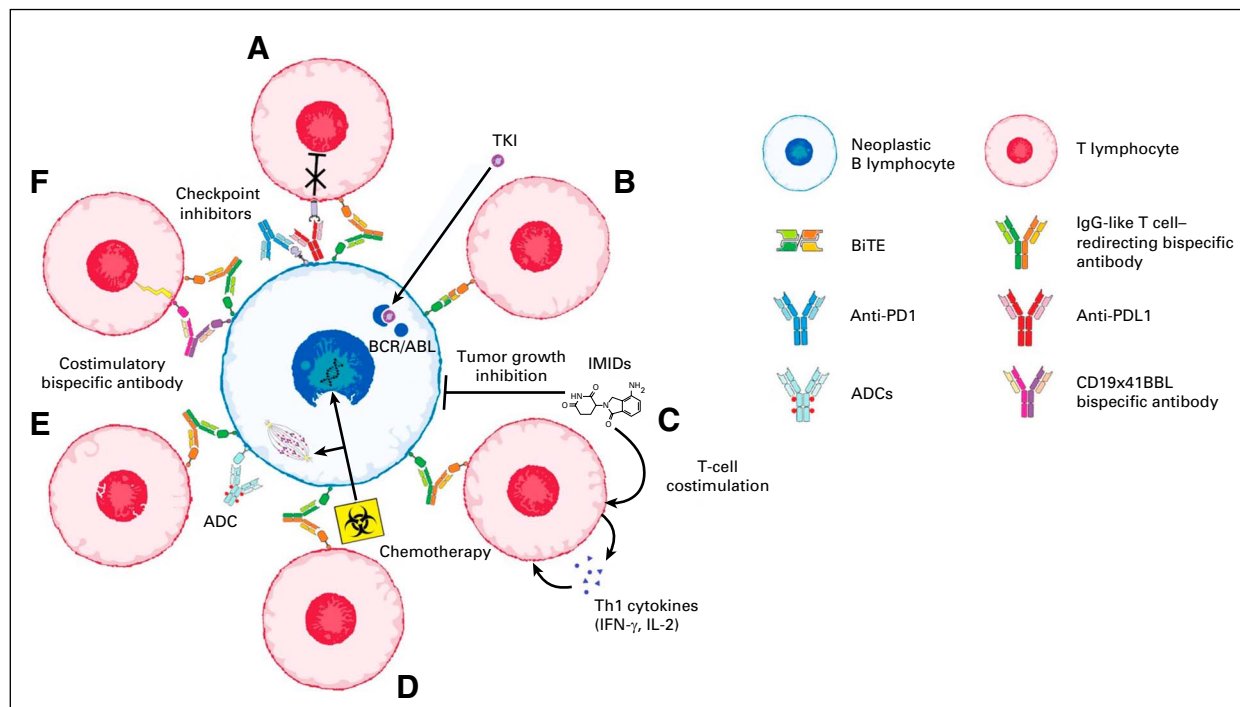
FIG 2. Combined use of T cell–redirecting bispecific antibodies in B-cell precursor acute lymphoblastic leukemia and B-cell non-Hodgkin lymphomas. Ongoing clinical trials (see Tables 2 and 3 for details) are evaluating the therapeutic activity of T cell–redirecting bispecific antibodies used in combination with (A) checkpoint inhibitors; (B) tyrosine kinase inhibitors (TKIs); (C) immunomodulatory drugs (IMIDs); (D) chemotherapy; (E) antibody-drug conjugates (ADCs); and (F) costimulatory bispecific antibodies.

In another phase II study, blinatumomab was evaluated as a bridge to autologous HSCT in patients with aggressive NHL not responding to platinum-based salvage therapy. Stepwise blinatumomab (9-28-112 μg/d) was given in a 70-day cycle and optional second 28-day cycle. Of the 41 patients enrolled, 68% were refractory to the first salvage therapy, and a high rate of discontinuation due to disease progression (41%) was observed during the first treatment cycle. Despite that the exposure to blinatumomab was lower than anticipated, the ORR after 12 weeks was 37% (CR, 22%), and 20% of patients subsequently received autologous transplantation.[49] Additional studies to treat residual disease with blinatumomab are ongoing in the front-line setting,[50] and an MRD-driven therapy for DLBCL post autologous transplantation was terminated early because of low accrual (ClinicalTrials.gov identifier: NCT03298412). In some patients, the response achieved by blinatumomab was durable. The long-term results of the first phase I study showed that patients treated with ≥ 60 μg/m² (n = 25) achieved an OS of 5.8 years, with six patients disease free after > 7 years.[51] In another study with patients with DLBCL, 62% of complete responders were alive at 18 months.[52] Thus, the meaningful long-term survival achieved with the first-in-class BiTE construct increases the hope that bispecific antibodies may lead to the cure of a proportion of chemotherapy-resistant NHL.

MECHANISMS OF RESISTANCE TO BLINATUMOMAB

Resistance to blinatumomab is attributable to characteristics of the disease or the patient's immune system or both. Loss of target antigen expression has been proposed as a common mechanism of resistance to either chimeric antigen receptor T cells (CARTs) or blinatumomab. In retrospective analyses, performed in patients experiencing treatment failure on blinatumomab, < 20% had ALL recurrence with CD19-negative blasts.[18,32,53] Alternative splicings or truncated CD19 variants can explain this loss of expression, but recently a disrupted CD19 membrane export in the post–endoplasmic reticulum compartment has been indicated as a possible molecular basis for CD19 loss on the cell surface.[54] A myeloid lineage switch is also possible, particularly in the case of KMT2A(MLL)-rearranged ALL.[55]

Alternatively, an excessive number of T regulatory cells (T-regs) can play a key detrimental role on the therapeutic effect of blinatumomab. A threshold of T-regs < 10% in the peripheral blood has been proposed to identify patients with the highest likelihood to respond to blinatumomab.[56] An increased expression of programmed death-ligand 1 (PD-L1) on T cells represents an additional potential immune escape mechanism.[57] Two studies are exploring if the addition of pembrolizumab to blinatumomab, to enhance the activity of T cells and hence of blinatumomab, will improve the ORR in adults with R/R BCP-ALL (ClinicalTrials.gov identifiers: NCT03160079 and NCT03512405).

It should be remembered that in ALL a bone marrow blast infiltration > 50% is associated with a reduced probability to achieve CR.[19] Thus, the optimal ratio between the CD3+ T cells and the target CD19+ cells is probably crucial.

These data have practical implications, because treatment strategies to tackle blinatumomab resistance may change according to the CD19 antigen loss. The therapeutic approaches may indeed vary from the combination of blinatumomab with checkpoint inhibitors[58-60] in CD19-positive relapses to the use of CARTs with different affinity for CD19.[61] The use of other immunotherapies, such as inotuzumab, in CD19-negative cases[62] or bicistronic CARTs targeting CD19 and CD22,[63,64] will be an alternative option.

NEW T CELL–REDIRECTED BISPECIFIC ANTIBODIES FOR B-CELL NHL

Although CARTs and checkpoint inhibitors rapidly achieved approval, no bispecific antibody has obtained an authorization market for NHL so far. Reasons for this delay included administration hurdles (ie, CI and need of repeated hospitalization) and difficulties in generating antibodies able to guarantee a relevant activity while avoiding immunogenicity.[51,65] New scFV-based molecules have been generated to enable a once-weekly dosing as the next-generation BiTE antibody constructs modified by fusion to an Fc domain (extend half-life BiTE).[66] However, near-physiologic half-life of > 10 days could be obtained by using a fully human or humanized immunoglobulin form, with or without a functional FC region (Fig 1). This was possible thanks to innovative technical solutions facing the issues of heterodimerization of heavy chains, as well as the correct coupling between heavy and light chains and the strategies of antibody purification.[8] Among these, the knob-into-hole technology was developed to solve the heavy-chain mispairing and allowed the generation of the full-length IgG1-like molecule with near-native architecture CD3xCD20 mosunetuzumab (CD20-TDB, RG7828, RO7030816).[67] The use of CrossMab technology, developed to allow a correct light chain mispairing, led to the generation of the 2:1 format bispecific antibody glofitamab (RG6026, CD20-TCB, RO7082859), in which two CD20 moieties are coupled with CD3.[68] Other proprietary technologies have been developed allowing the generation of the fully human IgG4 CD3xCD20 bispecific antibody odronextamab (REGN1979),[69] or the full-length CD3xCD20 bispecific IgG1 epcoritamab (GEN3013, Duo-Body-CD3xCD20).[70] Although all the IgG-like molecules discussed are provided by a nonfunctional FC portion, plamotamab (XmAb13676), a full-length CD3xCD20 bispecific antibody, was generated to permit the binding to FC receptor and thus enhance the T cell–mediated tumor killing.[71] Many other molecules are in a preclinical development[72]; hereafter, we will briefly overview the early clinical results so far available with the previously described new molecules (Table 3). Compared with blinatumomab, most of the IgG-like molecules have been associated with lower incidence of neurotoxicity, observed in 21%-44% of the patients (grade ≥ 3: 0%-4%), but higher CRS, occurring in 29%-59% of the cases (grade ≥ 3: 1%-6%).[73-77] With the aim to mitigate toxicity, additional strategies have been investigated. The increased antigen avidity of the 2:1 format of glofitamab allowed the use of anti-CD20 pretreatment to reduce antigen burden and, thus, toxicity.[74] The use of subcutaneous administration of epcoritamab was reported to induce less cytokine secretion in a preclinical model, and this potentially safer route of administration is under clinical investigation.[70,76] Beyond all the mitigation strategies adopted, CRS appears to be correlated with histology subtype and disease burden, with patients with bulky or leukemic disease being at higher risk. The future application of T cell–redirecting bispecific antibodies will largely depend on their improved safety profile and more practical and manageable delivery. It is worth noting the favorable toxicity profile of mosunetuzumab, which allowed its use also in the outpatient setting with severe CRS or neurological toxicity occurring in only 1% of cases.[73]

Early efficacy data from IgG-like molecules confirmed the capability of bispecific antibodies to induce promising ORR (Table 3). With the limitation of the nature of most studies (ie, phase I dose-escalation trials), the reported ORR and CR rate for R/R aggressive lymphoma is in the range of 37%-58% and 19%-42%, respectively. As expected, indolent lymphoma showed a marked sensitivity to immunotherapy, with ORR ranging from 63% to 95% and CR rate of 43%-77% in the R/R setting.[73-77] Most interestingly, bispecific antibodies were demonstrated to be active even in patients R/R to CD19-CART treatment and to be able to induce a second remission in those patients relapsing after achieving response to the first course of treatment.[73,75]

Emerging evidence is dissecting the pharmacodynamics of T cell–redirecting bispecific antibodies and could provide critical data to optimize the efficacy and dissociate activity from toxicity. Among the key findings, CD20 receptor occupancy proved to correlate with clinical response, thus informing the optimal biologic dose selection.[78-80] In addition, the capability of T cells to be efficiently activated appears to be critical for tumor eradication, and strategies to further unleash T-cell activity or restore T-cell functionality are currently under investigation.[81]

Although many clinical trials with T cell–redirecting bispecific antibodies for NHL are currently ongoing as single-drug use, several others are investigating their potential synergism with different agents (Fig 2; Table 3).[82,83] Suppression of T cell–mediated killing through PD-L1 was observed in NHL, and combination of checkpoint inhibitors with T cell–redirecting bispecific antibodies has been proved synergistic, preclinically.[84] Similarly, a rational combination seems to be the concomitant use of positive costimulations, as in the case of RO7227166, in which the

TABLE 3. Ongoing Clinical Trials With T Cell–Redirected Bispecific Antibodies in NHL

Drug	Phase	Clinical Setting	Results	Reference
Single-agent trials				
Blinatumomab	II	R/R indolent B-NHL	NR	NCT02811679
	II	Consolidation after first line in high-risk DLBCL	47 enrolled to R-CHOP, 28 treated with blinatumomab. Safety: NT, 61% (G > 3, 15%); Efficacy: ORR 89%, 94% of MRD negativity in 18 patients	NCT03023878[50]
	I	Subcutaneous use in R/R indolent B-NHL	NR	NCT02961881
	I	Consolidation after autologous HSCT in R/R DLBCL	NR	NCT03072771
	I	Consolidation after allogeneic HSCT in R/R CD19+ ALL and NHL	NR	NCT03114865
Mosunetuzumab (CD20-TDB)	I	R/R B-NHL (IV or SC single-agent cohort arm)	Safety: (n = 270) CRS, 29% (G3, 1%); NT, 44% (G3, 4%), ICANS-like, 1% (G3, 0%). Efficacy: aNHL (dose, 2.8-40.5 mg; n = 124) ORR, 37% (CR, 19%); iNHL (dose, 2.8-13.5 mg, n = 67) ORR, 63% (CR, 43%); Post CART (n = 18) ORR, 39% (CR, 22%); retreatment ORR, 75% (CR, 25%)	NCT02500407[73]
	I	DLBLC: < PR after first-line or unfit for first-line chemotherapy	NR	NCT03677154
Glofitamab (CD20-TCB)	I	R/R B-NHL (IV single-agent arm)	Dose 0.6-25 mg. Safety: (n = 88), CRS, 55% (G ≥ 3, 5%); NT, 16% (G ≥ 3 1). Efficacy: aNHL (n = 76) ORR, 46% (CR, 29%); FL (n = 8) ORR, 63% (CR, 50%)	NCT03075696[74]
Odronextamab (REGN1979)	I	R/R B-NHL	Safety: (n = 110), CRS, 59% (G3, 6%); NT, NR (mild). Efficacy: FL (dose ≥ 5 mg, n = 22): ORR, 96% (CR, 77%) DLBCL (dose ≥ 80 mg, n = 19): ORR, 58% (CR, 42%); DLBCL post CART (n = 12): ORR, 50% (CR, 25%)	NCT02290951[75]
	II	R/R B-NHL	NR	NCT03888105
Epcoritamab (GEN3013)	I/II	R/R B-NHL	Safety: (n = 31) CRS, 48% (G ≥ 3, 0%); NT, 0%. Efficacy: (n = 19) ORR, 37% (CR, 5%)	NCT03625037[76]
Plamotamab (XmAb13676)	I	R/R B-NHL, R/R CLL	Safety: (n = 53) CRS, 53% (G > 3 6%), NT, NR (mild). Efficacy: (80-170 μg/kg) DLBCL (n = 18) ORR, 39% (CR, 28%)	NCT02924402[77]
Combinatory trials				
Blinatumomab and pembrolizumab	Ib	Pediatric/young adult; R/R CD19+ ALL and NHL	NR	NCT03605589
	Ib	R/R DLBCL	NR	NCT03340766
Blinatumomab lenalidomide	Ib	R/R B-NHL	NR	NCT02568553
Mosunetuzumab and atezolizumab	I	R/R B-NHL (combinatory arm)	NR	NCT02500407
Mosunetuzumab and polatuzumab or bendamustine/polatuzumab/rituximab	I	R/R DLBCL or FL	NR	NCT03671018
Mosunetuzumab and CHOP or CHP-polatuzumab	Ib/II	R/R B-NHL (phase I); untreated DLBCL IPI 2-5 (phase II)	NR	NCT03677141
Glofitamab or mosunetuzumab and gemox	I	R/R DLBCL, R/R HGBCL	NR	NCT04313608

(continued on following page)

TABLE 3. Ongoing Clinical Trials With T Cell–Redirected Bispecific Antibodies in NHL (continued)

Drug	Phase	Clinical Setting	Results	Reference
Glofitamab or mosunetuzumab and lenalidomide	I	R/R FL	NR	NCT04246086
Glofitamab and obinutuzumab	I	R/R B-NHL (combination arm)	Safety: (n = 28) CRS 68% (G ≥ 3, 7%); NT, 18% (G ≥ 3 0%). Efficacy (16 and 10/16 mg cohorts): aNHL (n = 14) ORR, 71% (CR, 57%); FL (n = 4) ORR, 100% (CR, 100%)	NCT03075696[83]
Glofitamab and atezolizumab or polatuzumab	I	R/R B-NHL	Atezolizumab arm only. Safety: (n = 38) CRS, 45% (G ≥ 3, 0%); NT, 11% (G ≥ 3 0%). Efficacy: (dose ≥ 1.8 mg) aNHL (n = 21) ORR, 60% (CR 36%); iNHL (n = 4) ORR, 100% (CR 100%)	NCT03533283[82]
RO7227166 (CD19x41BB) and obinutuzumab or glofitamab	I	R/R B-NHL	NR	NCT04077723
Glofitamab and G-CHOP or R-CHOP	I	R/R B-NHL (dose escalation), untreated DLBCL (expansion)	NR	NCT03467373
Odronextamab and cemiplimab	I	R/R B-NHL	NR	NCT02651662

Abbreviations: ALL, acute lymphoblastic leukemia; aNHL, aggressive NHL; B-NHL, B-cell NHL; CART, chimeric antigen receptor T cells; CHOP, cyclophosphamide (Cytoxan), doxorubicin hydrochloride (Hydroxydaunorubicin), vincristine (Oncovin), and prednisone; CHP, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), and prednisone; CLL, chronic lymphocytic leukemia; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; G, grade according to Common Terminology Criteria for Adverse Events; G-CHOP, obinutuzumab-cyclophosphamide (Cytoxan), doxorubicin hydrochloride (Hydroxydaunorubicin), vincristine (Oncovin), and prednisone; HGBCL, high grade B-cell lymphoma; HSCT, hematopoietic stem-cell transplant; ICANS, immune effector cell-associated neurotoxicity syndrome; iNHL, indolent NHL; IV, intravenous; NHL, non-Hodgkin lymphoma; NR, not reported; NT, neurotoxicity; ORR, overall response rate; PR, partial response; R-CHOP, rituximab-cyclophosphamide (Cytoxan), doxorubicin hydrochloride (Hydroxydaunorubicin), vincristine (Oncovin), and prednisone; R/R, relapsed refractory; SC, subcutaneous.

potent T-cell costimulation (41BBL) is strictly dependent on tumor antigen (CD19).[85] Other strategies to costimulate T cells are represented by the combination with immunomodulatory agents such as lenalidomide. The investigation of the concomitant targeting of different antigens by adding antibody-drug conjugate is also ongoing. Last, the combination with standard chemoimmunotherapy may also provide evidence of synergism and may lead to the improvement of the most common first-line treatment schema (Fig 2; Table 3).

In conclusion, the innovative technology initially proposed by blinatumomab and then followed by other different forms of bispecific antibodies is changing the paradigm of immunotherapy and may represent a robust alternative to cellular therapy such as CARTs. Many issues remain open, such as the optimization of the pharmacokinetics of these compounds and a better control of toxicity that currently limits the treatment efficacy, particularly in NHL. The use of these drugs in combination or sequentially with chemotherapy, stem-cell transplantation, or other immune modulators most likely will improve the outcome of both ALL and NHL. In the years to come, with the intent to increase the efficacy and reduce the toxicity of intensive chemotherapy in both pediatric and adult high-risk patients, these novel immunotherapies will be specifically selected to maximize their benefit in different patient subsets. Most likely, BiTEs will be incorporated into the earlier phases of treatment (ClincalTrials.gov identifiers: NCT03367299 and NCT03792633), leaving a wider therapeutic role to CARTs in the R/R setting.[86,87] Overall, the therapeutic landscape will likely change, particularly in some molecularly specific disease subsets, where target therapies combined with immunotherapy will reduce the role of chemotherapy and improve the outcome. In general, the clinical benefit will not be limited to the younger and more fit patients but will also apply to older and more frail patients.[45,62]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Immunotherapy of Acute Lymphoblastic Leukemia and Lymphoma With T Cell–Redirected Bispecific Antibodies

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