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Review Article

Blinatumomab in the Therapy of Acute B-Lymphoid Leukemia

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Abstract. Blinatumomab, a CD19-CD3 bispecific T cell engager (BiTE), has two recombinant single-chain variable fragments that temporarily link $CD3^+$ T cells and $CD19^+$ B cells, leading to the T cell-mediated lysis of neoplastic B cells. Improved minimal residual disease (MRD)-negative response rates and long-term overall survival have been observed in B-ALL patients who received this drug. These therapeutic successes have led to FDA approval for refractory/relapsed and MRD-positive B-ALL patients. Furthermore, recent studies in newly diagnosed B-ALL patients have led in Philadelphia chromosome-positive patients to the development of chemotherapy-free regimens based on tyrosine kinase inhibitors plus Blinatumomab and in Philadelphia chromosome-negative patients to improvement in outcomes using chemotherapy regimens that have incorporated Blinatumomab in the consolidation phase of treatment.

Keywords: Blinatumomab; ALL; Immunotherapy; Bispecific antibody.

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Introduction. The development of bispecific antibodies (bsAbs) has represented an area of considerable interest in the past decade, related to their unique properties compared to traditional monospecific monoclonal antibodies.[1-2] Thus, a consistent number of bsAbs has been approved for cancer therapy, thus showing the rapid evolution of these antibodies as a novel category of therapeutic agents.[1-2]

T cell engagers (TCEs) are bsAbs that specifically bind to a tumor cell surface antigen and to the CD3 chain of the TCR and have the property of specifically activating an immune response T-cell mediated at the level of sites of tumor development..[1,2] Blinatumomab, an example of next-generation TCE, requires simultaneous spatial binding of the targets: CD19 on the surface of leukemic cells and CD3 on the surface of T cells.[1,2]

It is designed to lack an Fc portion, composed of the tandem scFv-based CD19xCD3 antibody, which was first approved in 2014 for the treatment of relapsed/refractory B-ALL and which is giving growing contributions to the treatment of these leukemic patients in various clinical settings.[3]

Blinatumomab in Relapsed/Refractory B-ALL. Blinatumomab was approved for use in patients with relapsed/refractory B-ALL based on single-group trials showing enhanced efficacy and acceptable safety profile. A large phase III trial explored a consistent group of 376 adult Ph^- R/R B-ALL patients randomly assigned to treatment with Blinatumomab or chemotherapy. Blinatumomab significantly improved OS with respect to chemotherapy (7.7 months vs 4.0 months, respectively) and event-free survival, as well as median

Table 1. Main clinical trials evaluating the safety and the efficacy of Blinatumomab in adult and pediatric R/R B-ALL.

Study	Blinatumomab design	Number of patients	Median age (years) (range)	CR rate %	MRD negativity	Overall Survival	EFS RFS DFS	CRS % NE %
TOWER, phase III, randomised[4]	R/R B-ALL patients randomised to chemotherapy or Blinatumomab	405 (total) 134 (chemo) 271 (Blina)	41 (18-80)	16 (chemo) 34 (Blina)	In patients in CR: 48% (chemo) 76% (Blina)	4.0 mo (chemo) 7.7 mo (Blina)	EFS: 4.6 mo (chemo) 7.7 (Blina)	CRS: 0 (chemo) 4.9 (Blina) NE: 8.3 (chemo) 9.4 (Blina)
Pooled analysis of 5 different trials[18]	R/R B-ALL	683 166(pediatric) 517(adult)	33 Pediatric 8.3 (0-17) Adult 41 (18-80)	Pediatric <50% bBMB 65% >50% bBMB 38% Adult <50% bBMB 69% >50% bBMB 34%	Pediatric <50% bBMB 51% >50% bBMB 25% Adult <50% bBMB 54% >50% bBMB 27%	Pediatric <50% bBMB 48% >50% bBMB 32% Adult <50% bBMB 33% >50% bBMB 21%	EFS Adult <50% bBMB 20% >50% bBMB 10%	CRS <50% bBMB 1% >50% bBMB 4% NE <50% bBMB 7.6% >50% bBMB 8.2%
Phase III randomized clinical trial 20120215[12,13]	Open-label phase III trial in Ph$^-$ patients, high-risk, first relapse post-induction and two consolidation cycles, MRD-positive	104 Randomized to receive chemotherapy or Blinatumomab 57 Chemo 54 Blino	5.5 (1-17)	NR	54% Chemo 90% Blina	4-yr OS 27% Chemo 59% Blina	4-yr EFS 43% Chemo 69% Blina	CRS 2% (Chemo) 5.6% (Blina) NE 2% (Chemo) 3.7% (Blina)
RIALTO Phase II[11]	R/R B-ALL patients received up to 5 cycles of Blinatumomab	110	8.5 (0.4-17)	52%	52%	14.6 months MDR$^-$ NE MDR$^+$ 9.3 m	RFS 8 months MDR$^-$ 8 m MDR$^+$ 2.8 m	CRS 1.8% NE 3.6%
ALL1331 Phase III[14]	Low-risk B-ALL treated with chemo alone or chemo plus Blinatumomab	255 174 BM±EM 81 IEM	(1-30) 10 Chemo 11 Blina	NR	NR	4-yr OS Blin 90.4% Chemo 79.6% Blin 97% Chemo 72% Blina 76% Chemo 68%	4-yr DFS Blin 61.2 % Chemo 49.5% Blin 84% Chemo 53% Blina 36% Chemo 38%	CRS 3% (Blina) NE 5% (Blina)

duration of remission (**Table 1**).[4]

The analysis of long-term survival of a large group of R/R, Philadelphia-negative, B-ALL patients enrolled in two phase II studies involving the treatment with Blinatumomab showed a mOS of 7.5 months; importantly, both OS and RFS plateaued with 3-year.[5] For patients who achieved a CR with Blinatumomab, followed by allogeneic HSCT while in remission, the mOS was 18.1 months.[5] About 17% of R/R B-ALL patients treated with Blinatumomab survived >36 months, including 55% of patients who underwent aHSCT and 45% without transplantation. The retrospective analysis of 532 R/R B-ALL patients treated with Blinatumomab who received this drug as first salvage had a longer mOS and RFS and higher rates of remission, MRD response, and aHSCT in continuous remission compared to those who received Blinatumomab as second or later salvage.[6]

The retrospective observational study (NEUF) explored the safety and efficacy of Blinatumomab in R/R patients evaluated in the context of real-world use of this drug in current clinical practice; 140 R/R B-ALL patients were evaluated (106 Ph$^-$ and 34 Ph$^+$).[6] This real-world data set of adult R/R B-ALL patients treated with Blinatumomab confirms the efficacy outcomes observed in randomized clinical trials.[7]

A phase I clinical study evaluated the safety and efficacy of Blinatumomab in combination with PD1 and CTLA4 inhibitors in R/R B-ALL patients.[8] Among 22 evaluable patients, the CR was 68%, and all achieved

MRD negativity: at 1 year, the RFS was 27%, and the OS was 63%.[8] These observations showed that combination therapy with Blinatumomab and immune checkpoint inhibitors (ICIs) in R/R B-ALL patients was safe and was associated with a high rate of MRD-negative responses. However, these results are only preliminary and required to be confirmed.

An open-label, single-arm, phase II, multicentre ALCANTARA study explored the response of 45 B-ALL Ph^+ patients who had relapsed or were refractory to at least one TKI to Blinatumomab.[9] 16/45 patients achieved a CR within the first two cycles of Blinatumomab therapy; mOS was longer in patients who achieved a CR than in those without CR; 14/16 patients in CR achieved complete MRD response; the median duration of complete MRD response was 9.7 months.[9]

The efficacy of Blinatumomab retreatment after relapse was evaluated. Thus, Topp et al. evaluated 11 B-ALL patients who received Blinatumomab retreatment after initial response and relapse. 4/11 patients responded to the retreatment with a mOS of 9.4 months.[10] Grade ≥3 neurologic events were observed in 3 patients.[10] These observations suggest that Blinatumomab retreatment may represent a reasonable treatment for relapse in patients who have responded initially to Blinatumomab.

In the pediatric setting, Locatelli and coworkers reported the results observed on 110 R/R pediatric B-ALL patients treated with 5 cycles of Blinatumomab, showing a good safety profile with a low incidence of grade 3 or 4 of cytokine release syndrome and adverse neurologic events; a response rate not affected by the presence of adverse cytogenetic/molecular abnormalities; mOS was significantly better for patients achieving a CR with MRD negative status compared to those who remained MRD-positive (not estimable vs 9.3 months, respectively); the 1-year probability was significantly better for patients who received aHSCT after Blinatumomab compared to those without aHSCT.[11]

In a phase III randomized clinical trial, pediatric high-risk, first-relapse B-ALL patients received Blinatumomab as consolidation therapy, administered before allo-HSCT, resulting in improved EFS and MRD remission rate compared to chemotherapy, with EFS benefit being observed in all subgroups of patients, including those with extramedullary disease and very early relapse (<18 months).[12] A longer follow-up of these patients showed a markedly better OS among patients treated with Blinatumomab compared to chemotherapy, independently of the MRD status before treatment.[13]

The Children's Oncology Group ALL 1331 phase III trial compared the survival of patients with low-risk first-relapse of B-ALL treated with chemotherapy alone or chemotherapy plus Blinatumomab.[14] For children, adolescents, and young adults with B-ALL in first relapse, there was no statistically significant difference in DFS and OS between the Blinatumomab and standard chemotherapy arms in an analysis performed considering the whole population of patients enrolled in the study. However, when the analysis was restricted to patients relapsing either at the level of bone marrow with or without extramedullary disease, a significant improvement in mOS was observed in the group of patients treated with Blinatumomab compared to chemotherapy alone (4-year OS rate 97.1% vs 84.8%, respectively).[14]

Inotozumab ozogamicin is an antibody anti-CD22-drug conjugate approved for the treatment of R/R B-ALL. A recent study showed that Inotuzumab, as well as Blinotumomab, may be used for clearing MRD in patients with B-ALL in remission after induction chemotherapy.[15] However, a part of patients treated with Inotuzumab or with Blinatumomab relapsed, and there is a rationale to treat these patients with both these two antibodies. Concerning R/R B-ALL patients, Fracchiolla and coworkers reported the study of 71 patients treated for different relapses with Blinatumomab and Inotuzumab; Blinatumomab represented the first treatment for 54 patients and Inotuzumab for 14 patients.[16] In the Blinatumomab/Inotuzumab group, after Blinatumomab, 65% of patients achieved a CR, with 42% of MRD negativity; in the Inotuzumab/Blinatumomab after Inotuzumab, 93% achieved a CR, with 46% of MRD negativity.[16]

A recent study by Jabbour et al. demonstrated that subcutaneous Blinatumomab displayed an efficacy comparable to that observed in studies involving intravenous Blinatumomab administration.[17] In this study, 29 R/R B-ALL patients were treated with two different schedules of subcutaneous Blinatumomab: using two cycles of subcutaneous Blinatumomab at 250-500 ug dose, 85% of patients achieved a CR, including 75% with MRD-negativity; Blinatumomab at 500-1000 ug dose, 92%% of patients achieved a CR, including 100% with MRD-negativity.[17] No treatment-related grade 4 CRS or neurologic events were reported.

In the study from Queudeville et al., through the analysis of five different trials involving the treatment of both adult and pediatric R/R B-ALL patients, patients were subdivided into two groups according to the number of bone marrow leukemic blasts (<50% and >50%). The proportion of patients achieving MRD negativity was significantly higher in patients with baseline lower tumor burden (<50% bBMB). OS and RFS were also significantly higher among patients with baseline lower leukemic burden (**Table 1**).[18] Adverse events related to grade 3 or more CRS are more frequent among patients with higher tumor burden (**Table 1**). In conclusion, a high leukemia burden before therapy limits the efficacy of Blinatumomab and lowering leukemic blast levels by <50% before starting Blinatumomab therapy is required to improve its efficacy.

The treatment of patients who are resistant or relapse after Blinatumomab therapy is a great challenge. One possible salvage therapy for these patients is represented by anti-CD19 CAR-T cells. Several studies have explored the sensitivity of these refractory/relapsing patients to CD19 CAR-T cells. An initial study by Pillai et al. based on the retrospective analysis of 166 patients who have undergone CD19-directed CAR-T cell therapy showed that prior therapy with Blinatumumab, observed in a part of these patients, was associated with a higher rate of failure to achieve MRD negativity or subsequent relapse with antigen escape.[19] A subgroup analysis performed in the context of the phase II ZUMA-3 trial involving the treatment of R/R B-ALL patients with CD19 CAR-T cells (Brexucabtagene autocel) showed in patients, who had prior Blinatumomab treatment, an overall CR of 60% compared to 80% observed in the patients without prior Blinatumomab.[20]

Myers and coworkers have performed a retrospective study on 420 pediatric B-ALL patients who received CD19-CART cells (mostly Tisagenglecleucel for R/R B-ALL); CR rates, EFS, RFS and OS, were comparable in blinatumomab-naïve (BLN) and blinatumomab-exposed patients who responded to Blinatumomab (BLR), thus indicating that Blinatumomab treatment does not preclude a response to CD19-CAR-T; however, CR, RFS, EFS and OS were reduced in blinatumomab-exposed patients who did not respond or did not achieve a CR following Blinatumomab treatment (BLNR).[21] An additional exploration of these patients showed that prior Blinatumomab nonresponse was associated with an increased frequency of CD19-negative relapses after CD19 CAR-T cell therapy.[22]

Gupta et al. have explored 157 R/R B-ALL adult patients treated with autologous CD19-directed Brexu-Cel (CAR-T cells); 88 of them received Blinatumomab prior to CAR-T cell therapy: 70% of these patients initially responded to Blinatumomab but then relapsed (BLR) and 30% did not respond to Blinatumomab (BLNR); the rest of patients was Blinatumomab-naïve (BLNV).[23] Rates of CR to CAR-T cell therapy were similar following therapy among BLR, BLNR and BLNV patients.[23] However, the 1-year OS was significantly better in BLNV and BLR compared to BLNR.[23] Furthermore, PFS was significantly higher in the BLNV group compared to BLR and BLNR.[23]

These observations, which need to be confirmed in larger, prospective clinical trials, support the conclusion that (i) CD19-targeted CAR-T cells represent an effective therapy for patients relapsing after an initial response to Blinatumomab; B-ALL patients who did not respond to Blinatumomab display shorter overall survival following CD19 CAR-T cell therapy compared to those who responded or did not receive Blinatumomab.

The possible therapeutic options for R/R B-ALL patients involving Blinatumomab are shown in **Figure 1**.

Blinatumomab for B-ALL in Remission MDR-Positive. Monitoring measurable residual disease (MRD) is a standardized and universally accepted

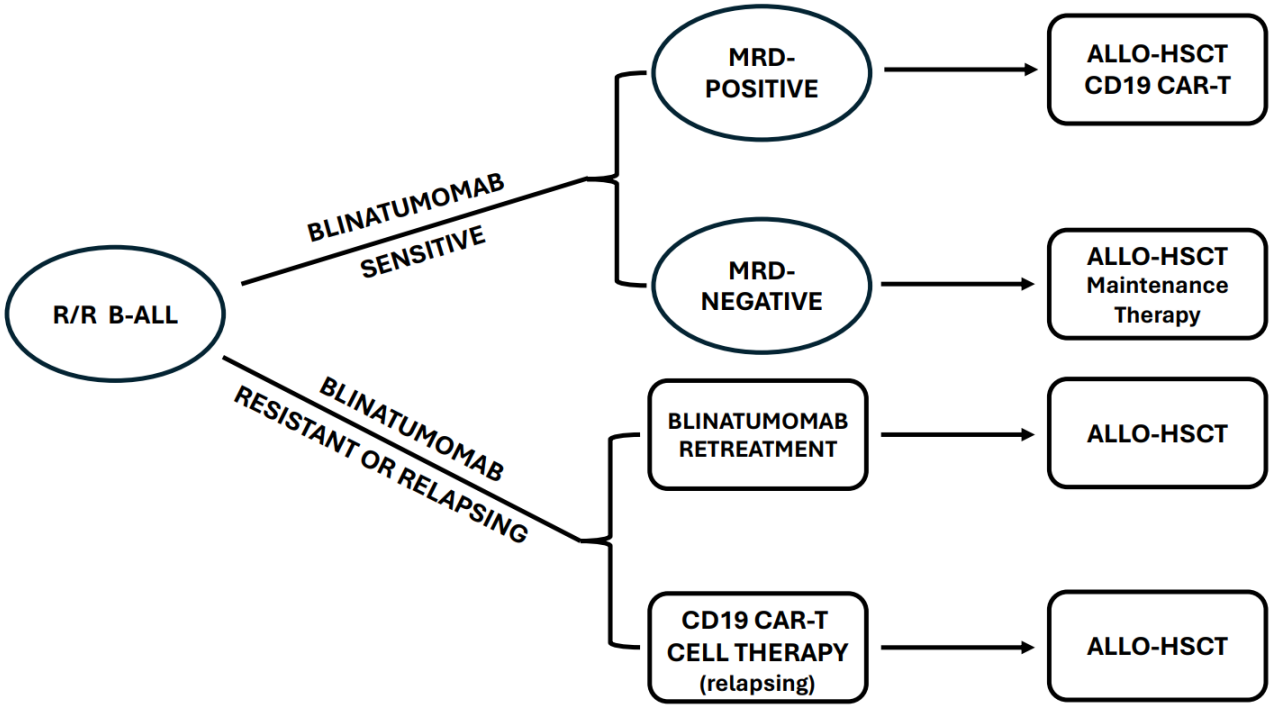

Figure 1. Therapeutic options for patients with R/R B-ALL involving first treatment with Blinatumomab: patients responding to this treatment and achieving a CR with MRD-positivity may underwent allo-HSCT or CAR-T cell therapy; patients resistant or relapsing after Blinatumomab treatment may be either retreated with Blinatumumab and patients responding to this salvage treatment may be allo-transplanted or treated with CD19 CAR-T cells and then with allo-HSCT.

method for measuring disease status in B-ALL patients, and it has become part of diagnostic patient care. MRD is a key independent predictor of the risk of relapse and long-term survival in both pediatric and adult B-ALL..[24] For virtually all B-ALL patients, it is possible to evaluate MRD, either using multi-colour flow cytometry (MCFC), quantitative polymerase chain reaction (PCR) to detect immunoglobulin gene rearrangements or specific fusion transcripts, and more recently, next-generation sequencing (NGS).[24] NGS is associated with high sensitivity and allows the detection of very low MRD levels ($<10^{-4}$).[24]

A first pilot study from the GMALL group evaluated whether Blinatumomab monotherapy could improve leukaemia-free survival in B-ALL patients with MRD persistence after induction and consolidation therapy.[24] 20% of patients were enrolled in the study, and 80% of them displayed a conversion from MRD positivity to MRD negativity.[20] In most patients, MRD negativity was achieved after 1 cycle of Blinatumomab. The probability of relapse-free survival was 78% at a median follow-up of 405 days.[25] In a single-arm study, after treatment with Blinatumomab in a population of 116 adult B-ALL patients predominantly Ph-negative, with MRD-positive ($\geq 10^{-3}$) disease, the median OS and RFS were significantly longer among patients achieving a complete MRD response, compared to those who remained MRD-positive (**Table 2**).[26] After a longer follow-up, mOS in all patients was 36.5 months, and it was not reached in MDR-negative patients, compared to 16.5 months in MDR-positive patients.[27] The 5-year survival showed a 43% survival for the whole population of patients and 50% for those achieving MRD negativity. Future studies will be required to identify patients who may benefit from Blinatumomab without HSCT, including older patients and those without a related or matched donor, and to identify therapeutic strategies that could improve outcomes further.

In another study, Gokbuget et al. evaluated the prognostic impact of MRD status after Blinatumomab treatment in 90 R/R B-ALL patients achieving a CR: patients with a CR and MRD negative status displayed a significantly longer OS and RFS compared to those with MRD positivity.[28] This study supported the predictive value of MRD evaluation in B-ALL patients treated with Blinatumomab.

In a phase II study, Jabbour et al. evaluated 37 B-ALL patients (27 in first complete remission and 10 in second complete remission) in CR with MRD-positive status ($\geq 10^{-4}$) and then treated with Blinatumomab: 73% of these patients achieved an MRD-negative remission.[29] Importantly, the 3-year RFS and OS rates were 51% and 61% in patients with baseline MRD$\geq 10^{-3}$ and 83% and 77% in patients with baseline MRD$<10^{-3}$ (**Table 2**).[29]

Based on these studies, the FDA granted accelerated approval and final approval for Blinatumomab in 2018 and 2023 for the treatment of adults and children with B-ALL in first or second complete remission with MRD greater than or equal to 0.1%.

Cabanes-Hamy et al. retrospectively evaluated 73 patients who received treatment with Blinatumomab either in the first CR with MRD positivity or at relapse; high pre-Blinatumomab MDR levels were associated with shorter RFS and OS.[30] In relapsed patients, those who directly received Blinatumomab had shorter RFS and OS than patients bridged to Blinatumumab after chemotherapy treatment.[30]

Two other retrospective studies have further supported the efficacy of Blinatumomab in MRD-positive B-ALL patients. In the NEUF retrospective observational study, 109 adult MRD-positive B-ALL patients were included (83 Ph^- and 26 Ph^+); in this group of patients, within the first cycle of Blinatumomab treatment, 93% of Ph^- and 64% of Ph^+ patients achieved an MRD response (MRD<0.01%).[7]

A recent real-world study reported the outcome of adult patients who received Blinatumomab in first or second complete remission.[26] Patients in CR1 received Blinatumomab mostly for MRD persistence or for the inability to receive standard consolidation therapy. A complete MRD response was achieved after one Blinatumomab cycle in 83% of CR1 and 86% of CR2; after a median follow-up of 3.1 years, the 3-yr cumulative incidence of relapse was 23% for CR1 and 26% for CR2.[31]

Blinatumomab in B-ALL Patients in Remission MRD-Negative. Patients with newly diagnosed B-ALL frequently relapse even when achieving complete remission and MRD negativity after chemotherapy treatment. Litzow et al. have explored a group of 220 B-ALL patients achieving CR with MRD negativity (defined as MFC-MRD <0.01%) after induction chemotherapy; these patients were randomized either to receive consolidation therapy based on chemotherapy alone or chemotherapy plus Blinatumomab.[32] Patients undergoing consolidation therapy plus Blinatumomab displayed a mOS significantly lower than those treated with chemotherapy alone.[32] The benefit deriving from Blinatumomab administration was more pronounced in patients <55 years, and the improvement of OS induced by Blinatumomab was observed both in the group of patients MRD-negative and those with MRD levels between undetectable and 0.01%.[28] The RFS in MRD-negative patients favored the Blinatumomab arm vs the chemotherapy arm.[33] Another subgroup analysis of these patients showed that the OS of patients who received 1-2 cycles of Blinatumomab displayed no significant difference compared with the controls.[34]

Gu and coworkers have explored the effectiveness of Blinatumomab in clearing NGS-measurable MRD in pediatric B-ALL patients.[35] To this end, 19 B-ALL

Table 2. Clinical trials exploring the safety and the efficacy of Blinatumomab in MRD-positive B-ALL patients at first or later CR.

Study	Blinatumomab design	Number of patients	Median age (years) (range)	MRD Negativity	Overall Survival	EFS RFS DFS	CRS % NE %	HSCT
BLAST, phase II[26,27]	Single-arm, open-label to evaluate safety and efficacy of Blinatumomab in adult B-ALL patients in CR with MRD≥10^{-3}	116 (total) 64% CR1 34% CR2 2% CR3 96% Ph^-	45 (18-76)	78% (after first cycle) 80% (after second cycle)	After a follow-up of 59.8 months mOS 36.5 mo MRD^- NR MRD^+ 16.5 mo Patients in CR1 41.2 mo Patients in CR 2 23.1 mo	After a follow-up of 29.9 months mPFS 18.9 mo MRD^- 23.6 mo MRD^+ 5.7 mo Patients in CR1 14.6 mo Patients in CR2 5.7 mo	NE 9% (first cycle) 3% (second cycle)	CRS: 0 (chemo) 4.9 (Blina) NE: 8.3 (chemo) 9.4 (Blina)
Phase II[29]	Prospective single-arm phase II study with adult B-ALL, MRD >10^{-4} after first or later CR	37 73% CR1 27% CR2,3 53% Ph^- 47% Ph^+	43 (22-84)	65% (after the first cycle) 80% (after the second cycle)	3-year OS MRD^- 72% MRD^+ 52% CR1 72% CR2 51% aHSCT 71% No-AHSCT 66%	3-year RFS MRD^- 66% MRD^+ 52% CR1 68% CR2 37% aHSCT 71% No-aHSCT 58%	CRS 3% NE 8%	41% allo-HSCT 10/15 with allo-HSCT surviving 12/18 without allo-HSCT and responding to Blinatumomab, surviving
Real-world study GRAALL group[30]	Retrospective analysis on B-ALL patients with CR, MRD-positive	35 MRD level >1% 28% 0.1-1% 30% 0.01-0.1% 28% <0.01% 14%	32 (17-74)	89%	mOS not reached 3-yr OS >1% 33% 0.1-1% 58% <0.1% 86%	mRF not reached 3-yr PFS >1% 33% 0.1-1% 58% <0.1% 78%	Not reported	66% allo-HSCT

pediatric patients, bearing at least one unfavorable genetic abnormality, such as *KMT2A* rearrangement, in hematological CR with MRD <10^{-4} after induction or consolidation chemotherapy; however, all these patients were identified as MRD-positive by NGS.[35] After Blinatumomab treatment, MRD negativity by MFC was 95%, and the NGS-MRD negativity rate at 10^{-6} was 68%.[37]

The possible therapeutic options involving Blinatumomab for patients achieving a CR after induction chemotherapy with either MRD-positive or MRD-negative condition are shown in **Figure 2**.

Blinatumomab and Hematopoietic Stem Cell Transplantation. Allogeneic hematopoietic stem cell transplantation (a-HSCT) represents a potentially curative approach for B-ALL patients, as well as for other hematologic malignancies. However, a significant proportion of B-ALL patients relapses after a-HSCT. These relapsing patients have a poor prognosis, and some studies have evaluated their response to Blinatumomab. Stein et al. evaluated the response of 64 B-ALL patients who relapsed after aHSCT and investigated the safety and efficacy of Blinatumomab.[36] 45% of these patients achieved a CR within two cycles of Blinatumomab treatment and 30% with a complete MRD response.[33] These observations have supported Blinatumomab as a valuable salvage therapy in relapsing B-ALL patients after aHSCT.[36]

Gaballa and coworkers have reported the result of a single center phase II study evaluating the administration of Blinatumomab during the first year after a-HSCT, with the main aim to mitigate relapse in high-risk B-ALL patients.[39] A comparison with a contemporary group of 57 B-ALL patients suggests no benefit from Blinatumomab administration.[39] Correlative studies suggested the classification of patients into responders and non-responders according to specific T-cell profiles.[37] It is important to note that in this study, B-ALL patients remained on immunosuppression during Blinatumomab treatment.[37] A more recent phase Ib/II trial evaluated the tolerability and the efficacy of Blinatumomab as post-aHSCT remission maintenance in B-ALL (19 patients) and NHL patients off immunosuppression.[38] The results showed that post-aHSCT maintenance therapy is feasible with minimal toxicity in patients off immunosuppression with 18% of relapses, all occurring at the level of the central nervous system.[38]

Chauvet et al. evaluated 72 B-ALL patients relapsing after aHSCT: 50 patients received Blinatumomab alone, and 22 patients received Blinatumomab plus donor lymphocyte infusion (DFI).[39] Two-year OS was not significantly different between these two groups of patients; PFS and adverse events were similar in the two groups of patients.[39] The observations suggest that the

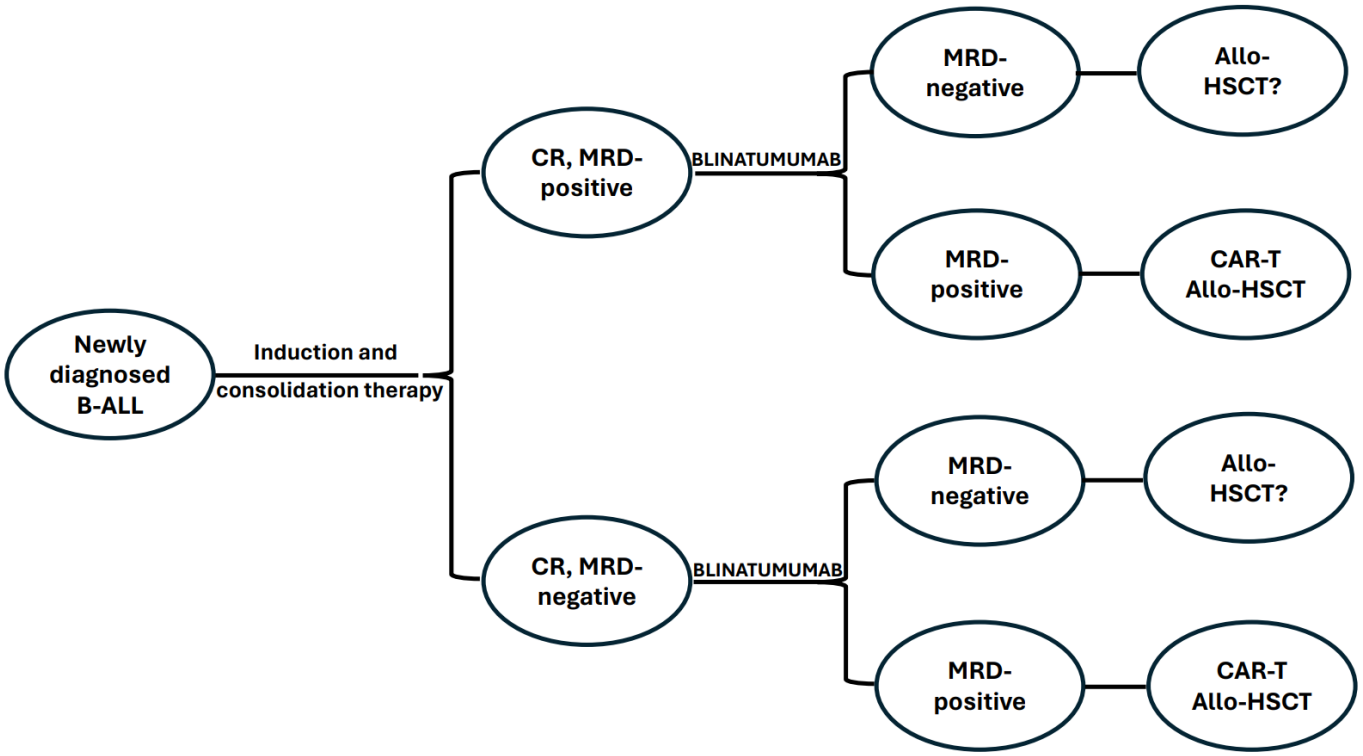

Figure 2. Therapeutic options for newly diagnosed B-ALL patients achieving a CR following induction and consolidation chemotherapy, with MRD-positive or MRD-negative disease are outlined.

DLI with Blinatumomab administration to B-ALL patients relapsing after aHSCT is safe but does not seem to improve outcomes.

Other studies have evaluated the administration of Blinatumomab pre-transplantation. There is a strong rationale for using Blinatumomab before aHSCT as a tool to clear MRD. In fact, residual MRD before HSCT is predictive of recurrence and thus, achieving MRD negativity before HSCT is a key strategy to improve and optimize the curative capacity of transplantation. Two randomized, phase III trials have shown the superiority of Blinatumomab compared to conventional chemotherapy as a consolidation treatment before aHSCT in pediatric patients with high-risk or intermediate-risk B-ALL, showing an improved disease-free survival, lower incidence of disease relapse post-HSCT and significantly reduced toxicity.[12,40] Furthermore, a post-hoc analysis of the study of Locatelli et al.[12] showed that a higher proportion of patients with high-risk first-relapse B-ALL with MRD positivity at the time of randomization achieved an MRD negative status after treatment with Blinatumomab compared with patients treated with intensive chemotherapy.[43] OS showed a strong benefit with Blinatumomab vs chemotherapy. Furthermore, Blinatumomab also improved outcomes for patients who had already achieved an MRD-negative condition prior to randomization.[41]

Sayyed and coworkers have explored 177 adult B-ALL patients undergoing aHSCT: 26.5% of these patients received Blinatumomab before HSCT, while the rest of the patients received chemotherapy.[42] Pretransplant Blinatumomab has been associated with improved OS and lower risk of non-relapse mortality in B-ALL patients undergoing HSCT, seemingly reflecting a lower burden of treatment-related toxicity in the Blinatumomab-treated population.[42] Multivariate analysis confirmed the association between pretransplant Blinatumomab and improved OS and NRM.[44] A similar study was performed on pediatric B-ALLs.[43]

Blinatumomab is Used in the Frontline Treatment of Philadelphia-Positive B-ALL. , the most frequent cytogenetic abnormality in adult B-ALL. Several recent studies have shown that it is possible to replace the chemotherapy backbone with Blinatumomab in association with TKIs.

In the LAL 0216 (D-ALBA) trial, the GIMEMA group explored the safety and efficacy of a chemotherapy-free regimen based on Blinatumomab plus Dasatinib in newly diagnosed Ph^+ B-ALL patients (**Table 3** and **Figure 3**).[46] In this study, 63 newly diagnosed B-ALL patients were treated first with an induction therapy based on Dasatinib plus glucocorticoids and then with two to five cycles of Blinatumomab and Dasatinib and 12 doses of intrathecal chemotherapy.[44] In an initial report of this study, at a median follow-up of 18 months, OS was 95% and DFS 88%.[44] Patients with IKZF1 deletion plus additional genetic abnormalities displayed a lower rate of DFS

Table 3. Clinical trials exploring the safety and the efficacy of Blinatumomab in newly diagnosed B-ALL patients, Ph^+ or Ph^-.

Study	Blinatumomab design	Number of patients	Median age (years) (range)	CR rate	MRD Negativity	Overall Survival	EFS RFS DFS	HSCT
GIMEMA LAL 2116 D-ALBA Phase II[44-45]	ND Ph^+ B-ALL Dasatinib induction for 85 days and then 2-5 cycles of therapy with Blinatumomab plus Dasatinib	63 newly diagnosed Ph^+ B-ALL	54 (24-82)	98%	Ater induction 29% After consolid. 60%	4-year 80.7% Patients with $IKZF1^{plus}$ have shorter OS	4-year DFS : 75.8% EFS : 74.6%	39%
Phase II NCT 02143414[46-47]	Dasatinib and Prednisone as induction therapy followed by Blinatumomab and Dasatinib for 3 cycles, followed by Dasatinib/Prednisone maintenance	24 newly diagnosed Ph^+ B-ALL	73 (65-87)	88% (after induction therapy) 95% (after Blinatumomab)	63% by RT-PCR	3-year OS 87% mOS 6.5 years	3-year EFS 77% mDFS not reached	Not compatible for the age of patients
Phase II NCT 03263572[49]	5 cycles of combined treatment with Ponatinib and Blinatumomab, followed by Ponatinib monotherapy.	60 40 Newly diagnosed Ph^+ (ND) 14 R/R Ph^+ B-ALL (R/R) 6 CML lymphoid blast phase (CML)	51 (36-68)	95% (ND) 85% (R/R)	87% (ND) 79% (R/R) 33% (CML)	2-year 89%	2-year EFS 77%	3%
GIMEMA LAL 2317 Phase II[59]	Adult Ph^- B-ALL patients treated with induction chemotherapy and then with six consolidation-therapy cycles; at cycles 3 and 6 Blinatumomab was added	149 12 KMT2A r 5 TCF3/PBX1 31 Ph-like	41 (18-65)	88% (after induction Ct) 18-40yr 90% 40-50yr 92% >55yr 64% 95% (after Blinatumomab)	70% (after induction Ct) 93% (after Blinatumomab)	71% 18-40yr 76% 40-50yr 74% >55yr 49%	DFS 66% 18-40yr 71% 40-50yr 62% >55yr 42% CIR 27.5% MRD^- 17.5% Ph-like 42.5%	Not Reported
GRAAL-2014-QUEST Phase II[60]	B-ALL patients in remission after induction and consolidation 1, received treatment with Blinatumomab	95 High-risk Ph^- B-ALL	35 (18-60)	82%	Pre-Blina MRD<0.01% 56% Post-Blina MRD<0.01% 74%	Follow-up 18 months 92%	Follow-up 18 months DFS 78%	42%
GRAAL-2014-QUESTB Phase II[61]	Blinatumomab was administered during consolidation to adult Ph^- B-ALL patients and compared to a group of patients receiving only chemotherapy during consolidation	198 104 Chemotherapy 94 Blinatumomab	34 (18-59)	100% (before treatments)	After consolidation 2 72% (Blina) 76% (Chemo)	2.5 years 79% (Blina) 76% (chemo)	2.5 years DFS 72% (Blina) 54% (Chemo) 2.5 years CIR 20% (Blina) 41% (Chemo)	47% (Blinatumomab) 37% (Chemotherapy)

compared to patients without these genetic aberrations.[44] A recent update of the study reported the long-term results of this study with a median follow-up of 53 months.[45] After induction therapy, there was a difference in DFS and OS between patients with MRD-positivity and MDR-negativity. However, after two cycles of Blinatumomab, no significant differences in DFS and OS between molecular and nonmolecular responders were observed, thus suggesting that Blinatumomab is effective in preventing a relapse also in patients with MRD-positive disease after induction therapy.[47] Patients with MRD-positivity received an aHSCT.[45] These observations support the capacity of a chemotherapy-free regimen based on Dasatinib and Blinatumomab to induce durable long-term hematologic and molecular responses in adult Ph^+ B-ALL patients.[45]

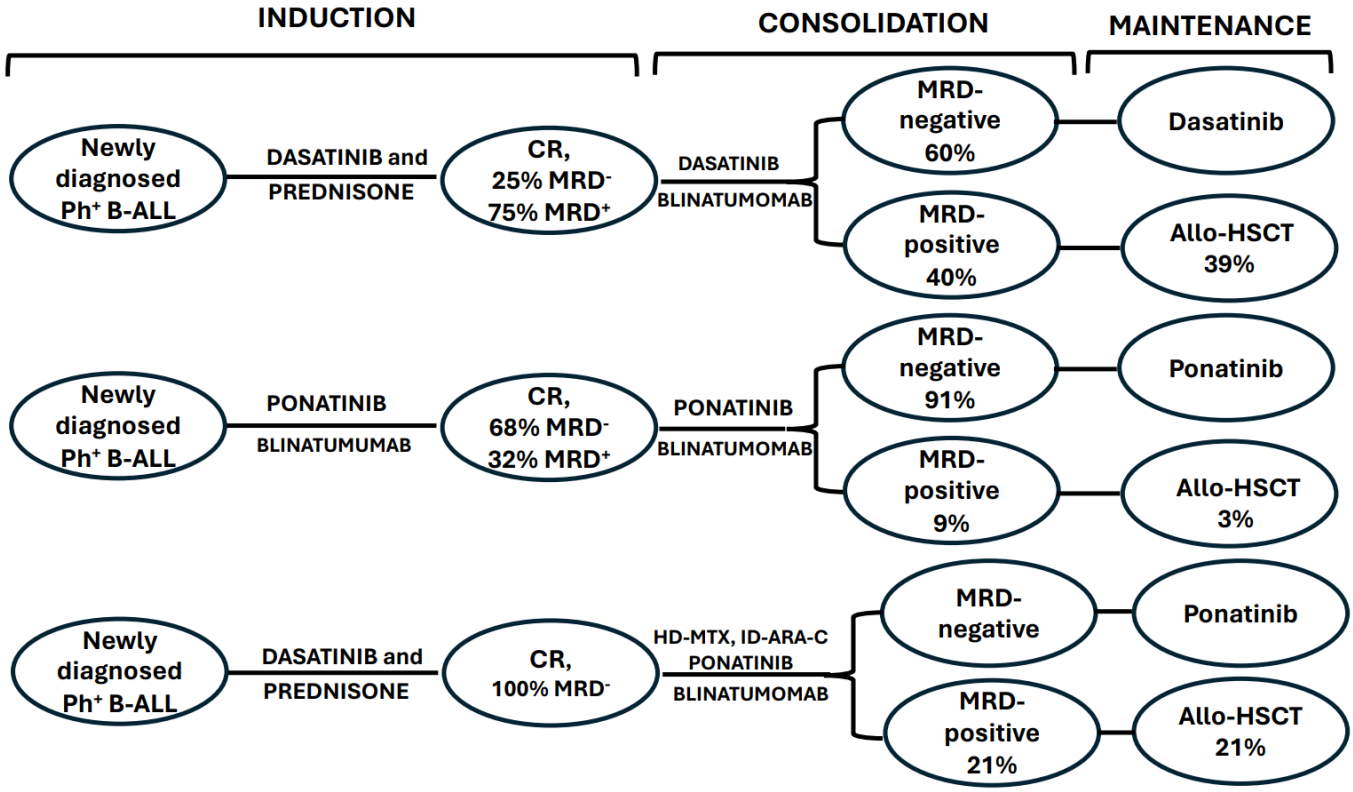

Figure 3. Outline of the main clinical trials involving the treatment of newly diagnosed Philadelphia-positive with Blinatumomab. From the top to the bottom: top pane shows the outline of the chemotherapy-free GIMEMA LAL 2116 trial by Foà et al.;[44-45] middle panel shows the outline of the chemotherapy-free clinical trial NCT 03263572 trial by Jabbour et al.;[49-50] bottom panel shows the outline of the clinical trial by Schwartz based on Blinatumomab and chemotherapy by Schwartz et al.[58]

Advani and coworkers have reported the results of a clinical trial carried out in 24 older (65 years of age or older) Ph^+ B-ALL with newly diagnosed disease or R/R disease, treated with induction therapy based on Dasatinib/Prednisone: patients achieving a CR continued this treatment up to day 84, while those not achieving a CR after day 56 attempted a re-induction treatment plus one cycle of Blinatumomab, followed by 3 cycles of post-remission therapy based on Blinatumomab and Dasatinib and maintenance therapy always based these two drugs (**Table 3**).[46] This study showed that this therapeutic regimen was safe and feasible.[46]

A phase II study designed Blinatumomab as a chemotherapy-sparing strategy in patients with Ph^+ B-ALL (BLISSPHALL). For patients in CR, Blinatumomab was used as early as 6 weeks into treatment, with the aim of accelerating MRD clearance and suppressing resistant clones early in the disease course. A maintenance phase based on Blinatumomab plus Dasatinib was included for patients in molecular complete response (CMR).[48] A strategy to suppress T315I clones and reduce their recurrence in the CNS could be achieved by combining third-generation TKIs or chemotherapy with Blinatumomab.

A single-centre, single-arm, phase II study enrolled 60 B-ALL patients with newly diagnosed or R/R B-ALL or chronic myeloid leukemia in the lymphoid blast phase and received treatment with the combined administration of Ponatinib and Blinatumomab for up to five cycles of treatment.[49] (**Table 3** and **Figure 3**) With a median follow-up of 16 months, 87% of patients with newly diagnosed B-ALL had a complete molecular response, and 79% of patients with R/R Ph^+ B-ALL had a complete molecular response.[49] In an updated analysis, 62 patients with newly diagnosed B-ALL were included, of whom 55 patients were available for molecular response; 84% achieved a complete molecular response; the 2-year OS was 89%, and EFS was 77%.[50]

In the GIMEMA ALL2820, whose preliminary results were recently reported, Dasatinib was replaced by Ponatinib, which was administered for 70 days together with steroids, followed by ≥2 cycles of Blinatumomab consolidation and 15 doses of intrathecal chemotherapy.[51] The maintenance therapy consisted either of Ponatinib or aHSCT for MRD-positive or $IKZF1^{plus}$ patients. At the end of the induction therapy, 95% of patients achieved complete hematological remission; with a median follow-up of 6.1 months, only one relapse was observed ($IKZF1^{plus}$ with T315I mutation).[51]

Olvermbatinib is a novel third-generation TKI that has been demonstrated to effectively target a wide range of BCR-ABL1 kinase mutations, particularly T315I, in CML patients and B-ALL patients.[52] Olvermbatinib, in association with chemotherapy[53] or with Blinatumomab,[52,54] was active in treating B-ALL patients who have failed TKI-based regimens, including T315I-mutated cases. Zhang et al. have reported the

results on the treatment of 13 B-ALL patients (11 Ph^+ and 2 Ph-like) with Olvermbatinib and Blinatumomab for one cycle of treatment (both administered during the induction phase), with 72.7% of patients achieving a CMR.[55]

The combination of Ponatinib with hyper-CVAD chemotherapy resulted in high rates of complete molecular remission and survival.[56] A recent phase II study explored in Ph^+ B-ALL patients the safety and the efficacy of a therapeutic regimen based on the sequential combination of low-intensity chemotherapy mini-Hyper-CVD and Ponatinib followed by Blinatumomab and Ponatinib.[45] Twenty patients were enrolled in this study, including 12 newly diagnosed B-ALL, 4 R/R B-ALL, and 4 lymphoid crises of CML. A high rate of complete molecular remission was observed.[57] With a median follow-up of 25 months, the rates of 2-year remission duration and OS in the newly diagnosed cohort were 90% and 82%, respectively.[57]

Schwartz et al. have reported the first results of a phase II clinical study involving the evaluation of consolidation with Ponatinib and sequential Blinatumomab and Chemotherapy after low-intensity Dasatinib-based induction in patients with newly diagnosed B-ALL (**Figure 3**).[58] 14 patients received initial induction treatment with Dasatinib plus prednisone until CMR was achieved; this treatment was followed by up to four cycles of consolidative chemotherapy (high-dose methotrexate and intermediate-dose cytarabine) plus Ponatinib and Blinatumomab; patients not proceeding to aHSCT continue Ponatinib monotherapy up to 5 years and 12 doses in intrathecal chemotherapy.[58] 21% of the patients underwent aHSCT at CR1. The results obtained in this study were compared to those observed in a historical group of patients treated in the same institution with Dasatinib induction treatment and aHSCT, and they showed a better RFS rate and a comparable OS rate.[58]

The studies on therapy of newly diagnosed Ph^+ B-ALL patients with either Dasatinib plus Blinatumomab or Ponatinib plus Blinatumomab indicate that these patients could be spared the toxicities associated with chemotherapy and the need for aHSCT in first response.

Blinatumomab in Frontline Treatment of Philadelphia-Negative B-ALL Patients. The outcome of adult B-ALL patients with Ph-negative B-ALL markedly improved following the introduction therapy of a chemotherapy regimen inspired by pediatric protocols associated with the evaluation of MRD at various time points during treatment, thus allowing a rational stratification of each patient or aHSCT, if required.

This treatment strategy inspired the phase II GIMEMA LAL2317 trial, and the study evaluated whether the introduction of Blinatumomab may improve the rate of patients achieving an MRD-negative status (**Table 3**).[59] In this study, adult Ph-negative B-ALL patients were treated with a pediatric chemotherapy backbone, with the introduction of two treatments with Blinatumomab after early consolidation cycle 3 and late consolidation cycle 6.[46] One hundred forty-nine patients were enrolled in this study. At the end of the induction period, 88% of patients achieved a CR, with a pronounced difference according to the age of the patients.[59] After early consolidation, 70% achieved an MRD-negative condition; the rate of MRD negativity increased to 93% after the first cycle of Blinatumomab treatment.[59] The OS was significantly better for patients achieving MRD-negativity. The cumulative incidence of relapse was 27.5%.[59] For patients achieving MRD-negativity, the cumulative incidence of relapse was 42.5% in Ph-like cases, compared to 17.5% in the remaining patients.[59] Factors affecting OS were the age of patients, CR achievement and MRD status observed after the first cycle of Blinatumomab.[59-60]

The GRAAL-2014-Quest study evaluated Blinatumomab in first-line in B-ALL defined as high-risk for one of these three conditions, including *KMT2A* rearrangements, *IKZF1* intragenic deletion or MRD-positivity post-induction.[61] High-risk B-ALL patients responding to induction treatment were enrolled in this study: patients with an aHSCT indication and a stem cell source received Blinatumomab until transplant for a minimum of 4 weeks; these patients received Blinatumomab during consolidation and maintenance therapy (**Table 3**).[61] MRD response was lower in patients with high pre-Blinatumomab MRD levels, while not impacted by age, WBC, or oncogenic subgroup; with a median of 20 months, 18-month DFS and OS were 78.8% and 92.1%, respectively.[61] Patients with a very high-risk condition (i.e., MRD <0.1% at 6 weeks or <0.01% at 12 weeks) displayed a worse DFS.[61] After an amendment, the modified study GRAALL-2014/B study included a group of patients receiving, when in remission with MRD>10^{-3} (or with >10^{-4} post-consolidation) Blinatumomab and a group of control patients undergoing only chemotherapy treatment as consolidation therapy (**Table 3**).[62] The median age of these patients was 34 years; 17% of them bear *KMT2A* rearrangements, and 40% *have IKZF1* deletion. Patients treated with Blinatumomab achieved a rate of MRD negativity higher than patients treated with chemotherapy alone.[62] A sub-analysis of this study showed that among high-risk B-ALL Ph-negative patients who benefit from Blinatumomab, there is a consistently heterogeneous landscape of response among genetic entities, with patients with *IKZF1* deletion exhibiting the most significant benefit from Blinatumomab of DFS.[63]

Several studies have associated the early use of Blinatumomab with a reduction of chemotherapy

intensity and burden. A phase II Australian Leukemia and Lymphoma Group (ALLG) evaluated reduced-intensity chemotherapy in combination with Blinatumomab. Thirty patients received debulking low-intensity chemotherapy with cyclophosphamide, vincristine and dexamethasone, followed by 7 days of Blinatumomab; the patients then received three alternating cycles of Blinatumomab and part B cycles of hyper-CAVD, followed by two years of maintenance therapy in patients and proceeding to aHSCT.[64] All treated patients achieved a CR.[64] 4 patients proceeded to aHSCT. The results appeared encouraging for older patients.[64]

The ALLG study group developed a trial to evaluate Blinatumomab in sequence with chemotherapy in a population of older, newly diagnosed B-ALL patients; in this study, Blinatumomab replaced three cycles of standard consolidation therapy.[65] Overall, the tolerability and efficacy of this regimen were very promising, with a high rate of hematologic and molecular responses.[53] In comparison with the current standard therapy, the MRD response rates were significantly better, and OS was superior to standard treatment.[65]

The multicentre, single-arm, phase II trial (NCT055557110) enrolled adult patients (15-59 years) with newly diagnosed Ph-negative B-ALL; the induction regimen comprised reduced-intensity chemotherapy, followed by two weeks of Blinatumomab.[54] The MRD negativity rate was 90.5% after 2 weeks of Blinatumomab.[66] Adverse events were rare, with 1/21 patients exhibiting grade 3 CRS and no patient displaying grade 3 or more neurologic events.[66]

A phase II study explored in 75 newly diagnosed Ph^- B-ALL patients the safety and the efficacy of a therapeutic regimen based on hyperCVAD alternating with high-dose methotrexate and cytarabine for up to 4 cycles, followed by 4 cycles of Blinatumomab at standard doses, in 37 patients Inotuzumab was added to 2 cycles of MTX/Ara-C.[55] In the whole population of patients (38 treated with HCVAD+Blina and 37 with HCVAD+Ino+Blina), the 3-yr OS was 88% and RFS 89%; the 3-year OS rate for patients without or with high-risk features was 93% and 83%, respectively.[67]

Two recent studies have explored the use of Blinatumomab in newly diagnosed pediatric B-ALL patients. In this context, van der Sluis and coworkers have evaluated the safety and the efficacy of Blinatumomab added to induction chemotherapy in 30 infants affected by *KMT2A*-rearranged B-ALLs. All 30 patients received the full course of Blinatumomab. 28/30 (93%) patients displayed either MRD-negativity (16 patients) or very low MRD levels ($<5x10^{-4}$) (12 patients) after Blinatumomab infusion. Two-year DFS and OS were 81.6 and 93.3% in this study and compared very favorably with the corresponding rates observed in the Interinfant-06 study based on chemotherapy alone.[68] In conclusion, this study showed that Blinatumomab added to the chemotherapy backbone used in the study Interinfant-o6 appeared to be safe and displayed high efficacy compared with historical controls.[68]

Schrappe and coworkers reported data on the safety profile of pediatric patients with high-risk B-ALL in first complete remission; after a 4-drug induction phase and two weeks of consolidation treatment, the patients were randomized to receive either two additional courses of consolidation chemotherapy or two 28-day courses of Blinatumomab.[69] The toxicity profile of Blinatumomab was more favorable to the intensive chemotherapy approach.[69] Outcome data are expected to demonstrate that the Blinatumomab arm is not inferior to chemotherapy.

Conclusions. The introduction of the bispecific CD19-CD3 antibody Blinatumomab in the treatment of B-ALL patients has significantly improved their outcomes, particularly those of adult B-ALL patients.

Studies carried out in R/R B-ALL patients in combination with chemotherapy improve RFS and OS and increase the frequency of patients who underwent an HSCT when in complete remission. Future studies will be required to define therapeutic strategies, such as a decrease of tumor burden before immunotherapy, to increase the number of patients responding to Blinatumomab. Importantly, patients relapsing after an initial response to Blinatumomab are clearly responsive to CD19 CAR-T treatment, while patients refractory to a previous Blinatumomab treatment are less responsive to CAR-T cells. Ongoing studies are evaluating the capacity of other drugs, such as Inotuzumab or ICIs, that, in combination with Blinatumomab, could improve its efficacy in R/R B-ALL patients.

Other studies have shown that Blinatumomab could represent an efficient therapeutic tool for clearing residual disease in B-ALL patients achieving a CR after induction chemotherapy with an MRD. In line with these observations, several studies have shown that there is a strong rationale for using Blinatumomab as a consolidation treatment before aHSCT. The consolidation therapy pre-transplantation with Blinatumomab improves RFS and OS compared to consolidation therapy based on chemotherapy only.

Several studies have explored the use of Blinatumomab in the first line of treatment for newly diagnosed Ph^+ or Ph^- B-ALL patients. The introduction of Blinatumomab in the first-line treatment of Ph^+ patients allowed to develop a chemotherapy-free approach based on the combination of Blinatumomab with a TKI (either Dasatinib or Ponatinib), resulting in high rates of complete molecular responses and long-term survival; the use of Ponatinib or other third-generation TKIs seems to reduce the rate of relapses related to generation/selection of resistant *ABL1*

mutations. These studies have shown that these chemotherapy-free treatments can spare the toxicities related to chemotherapy and reduce the need for aHSCT. The clinical studies carried out in newly diagnosed Ph$^-$ B-ALL patients showed a benefit of adding Blinatumomab, as supported by the achievement of high rates of MRD negativity, OS and DFS, better than those observed in historical controls. Future randomized clinical studies will be required to demonstrate the real improvement related to the addition of Blinatumomab to the chemotherapy treatment of Ph$^-$ newly diagnosed B-ALL.

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