High tumor burden before blinatumomab has a negative impact on the outcome of adult patients with B-cell precursor acute lymphoblastic leukemia. A real-world study by the GRAALL

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Abstract

Blinatumomab is a bispecific T-cell engager approved for B-cell precursor acute lymphoblastic leukemia (B-ALL) with persistent minimal residual disease (MRD) or in relapse. The prognostic impact of tumor load has been suggested before other immunotherapies but remains poorly explored before blinatumomab. We retrospectively analyzed the outcome of 73 patients who received blinatumomab either in first complete remission (CR) with MRD (n=35) or at relapse (n=38). Among MRD patients, 91% had MRD >0.01% before blinatumomab, and 89% achieved complete MRD response after blinatumomab. High pre-blinatumomab MRD levels were associated with shorter relapse-free survival (P=0.049) and overall survival (OS) (P=0.011). At 3 years, OS was 33%, 58% and 86% for pre-blinatumomab MRD >1%, between MRD 0.1-1% and <0.1% respectively. Among relapsed patients, 23 received blinatumomab with overt relapse and 15 were in complete response (CR) after bridging chemotherapy. At 3 years, overall CR rate was 68% and complete MRD response rate was 84%. Patients who directly received blinatumomab had shorter relapse-free survival (P=0.033) and OS (P=0.003) than patients bridged to blinatumomab. Three-year OS was 66% in the latter group compared to 16% in the former group. Our observations suggest that pre-blinatumomab tumor burden should help to design more tailored strategies including tumor load reduction in relapsed patients.

Introduction

The outcome of adult patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL) has been dramatically improved in the last decades by the use of pediatric-inspired chemotherapy regimen,[1-3] the risk stratification based on minimal residual disease (MRD),[4,5] and the introduction of tyrosine kinase inhibitor (ITK) in Philadelphia positive (Ph+) BCP-ALL.[6,7] More than 90% of patients below the age of 60 years achieve complete remission (CR) after induction with 5-year overall survival (OS) of about 60%. Early evaluation of MRD has been shown to be the most powerful prognostic factor associated with the risk of relapse.[4] A high MRD level after induction or during consolidation reflects a poor response to chemotherapy, and identifies patients that benefit from allogeneic hematopoietic stem cell transplantation (HSCT) in first CR.[5] Despite a global improvement in survival, about

30% of patients with Ph-negative BCP-ALL relapse, regardless of their age, with only 50% of second CR, and a poor long-term survival of around 10-20% at 5 years after relapse.[8]

Blinatumomab is a bispecific T-cell engager that recruits T cells on CD19-positive blast cells and induces anti-leukemic cytotoxicity. In a phase III study in patients with relapsed/refractory (R/R) BCP-ALL, blinatumomab showed a benefit over standard of care in terms of overall response rate and OS.[9] In a phase II study including MRD-postive (MRD+) patients, blinatumomab resulted in complete MRD response in 78% of patients after one cycle, and was associated with significantly longer relapse-free survival (RFS) and OS than MRD non-responders.[10] Among relapsed/TKI-refractory Ph+ BCP-ALL, blinatumomab showed anti-leukemia activity, with 36% of CR/CRh during the first two cycles, and 88% of complete MRD response among CR/CRh responders.[11]

Predictors of the response to blinatumomab were poorly investigated.[12] Recent studies suggested some BCP-ALL subgroups including *CRLF2*-rearranged ALL may be more sensitive to blinatumomab.[13] Whereas the absolute lymphocyte count is not correlated to the response, a high rate of regulator T cells may inhibit the cytoxicity redirected by blinatumomab.[14] Finally, the expression of specific CD19 isoforms lacking the epitope recognized by blinatumomab may also lead to primary resistance to this bispecific antibody.[13] As for other immunotherapies, the effector/target ratio is supposed to play a critical role in the efficacy of blinatumomab. However, the prognostic impact of leukemic tumor burden on the response to blinatumomab remains a matter of debate and confounding results emerged from comparisons treated at different disease stages.

The present study aimed to explore the role of pre-blinatumomab tumor load on patient outcome in a real-life cohort of patients treated between 2012 and 2016 for R/R or MRD+ adult BCP-ALL. The prognostic impact of pretherapeutic leukemic burden was investigated.

Methods

Study design

The present study is a retrospective, multicenter, case series study evaluating the efficacy and the tolerance of blinatumomab in adult patients treated for a BCP-ALL in the French compassionate use program. The study focuses on the impact of pre-blinatumomab tumor burden on patient outcome.

Inclusion criteria were: i) patients aged 15 years or more, ii) patients treated in the GRAALL network, iii) patients with Ph-negative or Ph+ BCP-ALL, in R/R to salvage therapy (R/R cohort) or in first or second remission with MRD+ (MRD+ cohort), iv) patients treated with blinatumomab in the French compassionate use (ATU: Autorisation Temporaire d'Utilisation) program. The study was registered as clinicaltrials gov. Identifier: NCT03751072 and was approved by an independent Ethic Committee, in accordance with the Declaration of Helsinki.

Response and safety assessment

Hematological CR was defined as <5% blasts in the bone marrow (BM) aspirates, with full hematologic recovery in the peripheral blood (neutrophil count >1×10^9/L and platelet count >100×10^9/L). Complete remission with incomplete hematologic recovery (CRi) was defined as <5% BM blasts with neutrophil count <1×10^9/L or platelet count <100×10^9/L. Complete MRD response was defined by the absence of detectable MRD, either by molecular immunoglobulin/T-cell receptor quantification, by flow cytometry (with sensitivity of 0.01%), or by BCR-ABL1 quantification in Ph+ ALL patients.

Statistical analysis

OS was defined as the time between blinatumomab first infusion and death, censoring patients alive at last follow-up. RFS was defined as the time between first blinatumomab infusion for MRD+ patients or the time of post-blinatumomab CR/CRi for relapsed patients and either death or relapse, censoring patients at last follow-up. In some analysis, OS and RFS were also censored at the time of HSCT. Univariate and multivariate analyses assessing the impact of pre-blinatumomab tumor burden were performed with a Cox model. Proportional hazards assumptions were graphically checked. MRD+ and relapse cohorts were analyzed separately. Statistical analysis was performed with the statistical software STATA/SE (Version 16.1, StataCorp LLC, College Station, Texas, USA).

Results

Patient's characteristics

Among the 80 patients who received blinatumomab in the French compassionate ATU program, 73 were included in this study from 11 GRAALL network centers (Figure 1). Thirty-five patients were in first complete remission (CR1) with persistent MRD (MRD+ cohort), and 38 were in first or subsequent relapse (relapse cohort). Patient in first CR1 were mostly treated according to GRAALL frontline protocols for Ph+ and Ph- BCP-ALL.[3,15] The choice of salvage therapy was left to the discretion of the treating clinician and many different schedules were used including weekly dosing of alkaloids and steroids, second-line ITK, hyper-CVAD, or pediatric-inspired regimen.

Patient's characteristics are summarized in Table 1.

The median age of the MRD+ cohort was 32 years (range,

17-74). At diagnosis, the median white blood cell count (WBC) was 8.1×10^9/L (range, 1.0-731.0). The karyotype showed a Philadelphia chromosome in three patients (9%), a *KMT2A* (formerly *MLL*) rearrangement in three patients (9%) and a low hypodiploidy/near triploidy in three patients (9%). An intragenic deletion of *IKZF1* gene was found in five of 19 screened patients (26%). Two patients had previously received an HSCT. Interim chemotherapy was given while waiting for treatment approval and delivery according to local investigator choice. Before blinatumomab infusion, only three of 32 (9%) patients had MRD <0.01%, and the majority (18/32, 56%) had MRD >0.1%.

The median age of the relapse cohort was 49 years (range, 16-74). Among these 38 patients, 11 had a Ph+ ALL (29%), two had a *KMT2A* rearrangement (6%), and three had a t(1;19) translocation. An *IKZF1* intragenic deletion was found in five of 21 evaluated patients (24%). Around two thirds of these patients received blinatumomab in first relapse (63%), and 15 of 38 (39%) had previously received an allogeneic HSCT. Due to local investigator decisions, patients could have received chemotherapy before blinatumomab. Among these 38 patients, 15 (39%) were in second or greater remission (CR2+) at the time of blinatumomab. Among these patients in CR2+, three of 11 (27%) had MRD of <0.01%, while the majority (7/11, 64%) had MRD of >0.1%.

Efficacy of blinatumomab in the minimal residual disease-positive cohort

Patients from the MRD+ cohort received a median of one cycle of blinatumomab (range, 1-2). Blinatumomab was started at the dose of 9 µg/day in ten of 24 patients (29%)

and 28 µg/day in the remainders (71%, 1 missing data). Among the 33 patients with available data, 23 received a premedication with dexamethasone (range, 20-40 mg total dose). Upon blinatumomab, a complete MRD response was observed in 31 of 35 patients (89%). Among the 35 patients, 23 (66%) proceeded to allogeneic HSCT in continuous CR. The median follow-up of this cohort was 3.6 years. A relapse was observed in six patients. Both the median RFS and OS were not reached (Table 2; Figure 2A and B). In this cohort, the 3-year RFS was 65% and the 3-year OS was 68%. When patients were censored at the time of HSCT performed in continuous CR after blinatumomab, the 3-year RFS was 71% and the 3-year OS was 77% (*Online Supplementary Figure S1A* and *B*).

Efficacy of blinatumomab in the relapse cohort

Patients from the relapse cohort received a median of one blinatumomab cycle (range, 1-5). CR was reached in 26 of 38 patients (68%, Table 2). Eleven of the 23 patients not in CR at the time of blinatumomab achieved CR (48%). Among the 26 patients in CR after blinatumomab, a complete MRD response was observed in 21 of 25 patients (84%) with no difference between patients in previous CR (12/14, 86%) or not (9/11, 82%, *P*=0.99). Twelve of 26 CR patients (46%) were bridged to allogeneic HSCT in continuous CR (Table 2). The median follow-up of this cohort was 3.3 years. The median RFS and OS were respectively 14.6 and 10.3 months (Table 2; Figure 3A and B). At 3 years, the RFS was 37% and OS was 35%. When follow-up was censored at transplant time, 3-year RFS was 38% and 3-year OS was 32% (*Online Supplementary Figure 2A* and *B*).
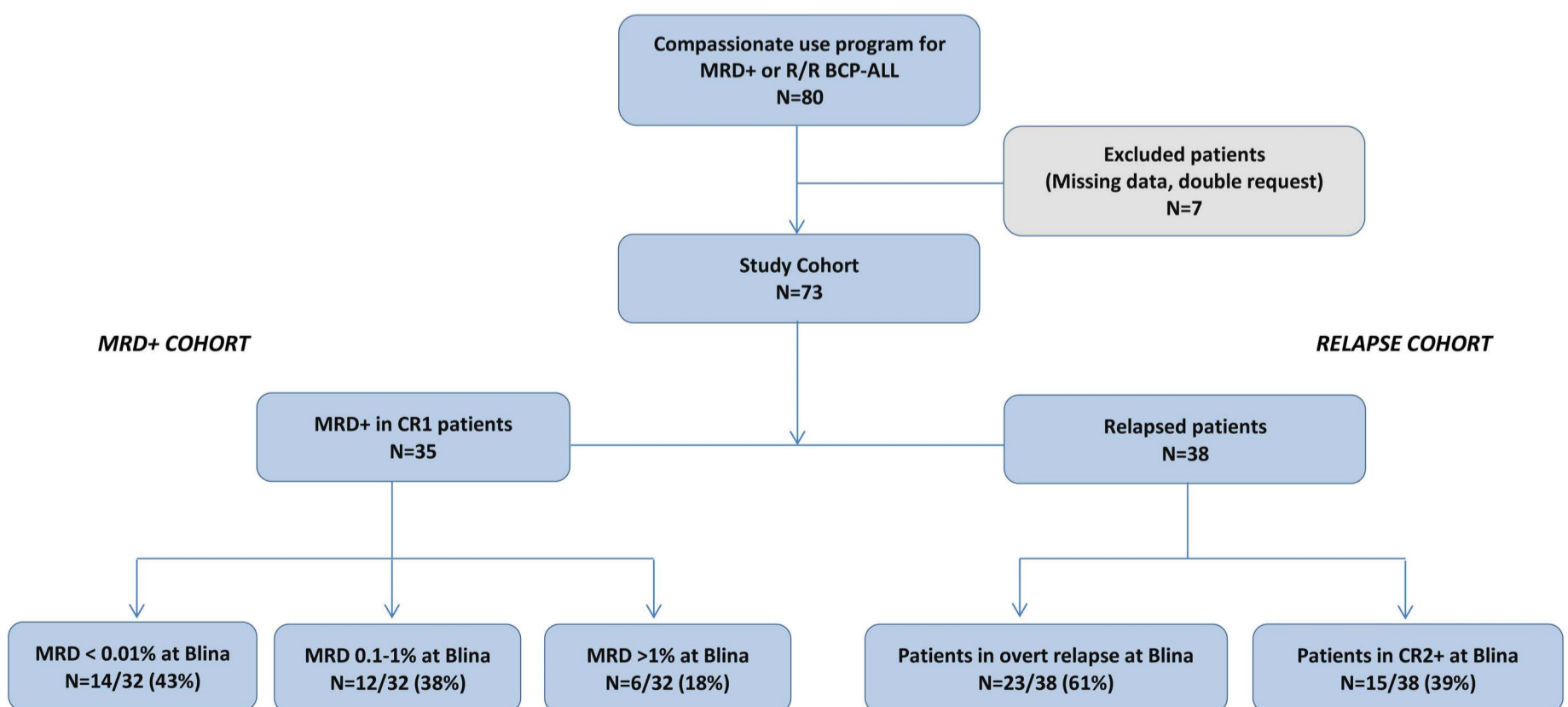
Figure 1. Flow-chart of the study population. CR1: first complete remission; CR2+: patients in second or greater complete remission; MRD: minimal residual disease; R/R: relapsed/ refractory; ALL: acute lymphoblastic leukemia.

Impact of pre-blinatumomab tumor burden on outcome

In order to address the impact of pre-blinatumomab tumor load on subsequent outcome, we first investigated the role of pre-blinatumomab MRD in the MRD+ cohort. Among the four patients who did not reach a complete MRD response after blinatumomab, two had a pre-blinatumomab MRD >1% (2/6, 33%) and two had MRD ≤1% (2/26, 8%; *P*=0.15). A high level of pre-blinatumomab MRD was significantly associated with a lower RFS and OS (Figure 4A and B). The 3-year RFS was respectively 33%, 58% and 78% respectively

for pre-blinatumomab MRD >1%, between MRD 0.1-1%, and <0.1% (*P*=0.049). The 3-year OS was 33%, 58% and 86% respectively for MRD >1%, between MRD 0.1-1%, and <0.1% (*P*=0.011). Of note, no difference in patient characteristics was observed between these three MRD subgroups (*Online Supplementary Table S1*). A multivariate analysis considering age, WBC at diagnosis, high-risk cytogenetics, and pre-blinatumomab MRD showed significantly shorter OS and RFS associated with higher MRD levels and a trend with high-risk cytogenetics (Table 3).
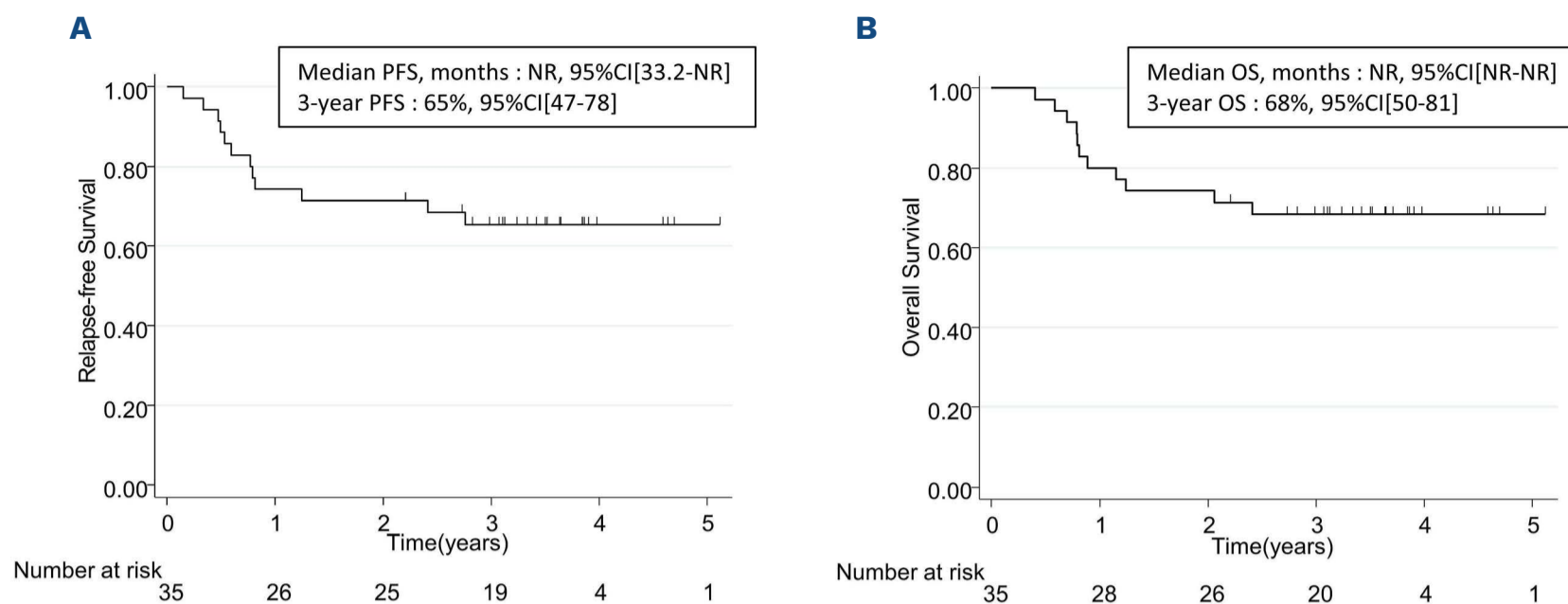
Table 1. Patient characteristics.

	All N=73	MRD+ cohort N=35	Relapse cohort N=38
Age in years, median (range)	42 (16-74)	32 (17-74)	49 (16-74)
Sex, male/female	43/30	21/14	22/16
WBC x10⁹/L, median (range)	8.1 (0.4-731.0)	8.1 (1.0-731.0)	8.2 (0.4-207.0)
Cytogenetics			
- t(1;19)/E2A-PBX1	3 (4)	0	3 (8)
- t(9;22)/BCR-ABL1	14 (19)	3 (9)	11 (29)
- *KMT2A*-r (*MLL*-r)	5 (7)	3 (9)	2 (6)
- low hypodiploidy / near triploidy	4 (6)	3 (9)	1 (3)
IKZF1 intragenic deletion, N (%)	10/40 (25)	5/19 (26)	5/21 (24)
Disease status			
CR1, n (%)	35/73 (48)	35 (100)	-
1ˢᵗ relapse, n (%)	24 (33)	-	24 (63)
≥ 2ⁿᵈ relapse, n (%)	14 (19)	-	14 (37)
Allo-HSCT before blinatumomab	17 (23)	2 (6)	15 (39)
CR at blinatumomab	50 (68)	35 (100)	15 (39)
% BM blasts, median (range)	0 (1-92)	1 (0-4)	2 (0-92)
MRD at blinatumomab (in CR patients), N (%)			
>1%	12/43 (28)	6/32 (18)	6/11 (55)
0.1%-1%	13/43 (30)	12/32 (38)	1/11 (9)
0.01-0.1%	12/43 (28)	11/32 (34)	1/11 (9)
<0.01%	6/43 (14)	3/32 (9)	3/11 (27)

WBC: white blood cell count; allo-HSCT: allogeneic hematopoietic stem cell transplantation: CR: complete remission; BM: bone marrow; MRD: minimal residual disease.
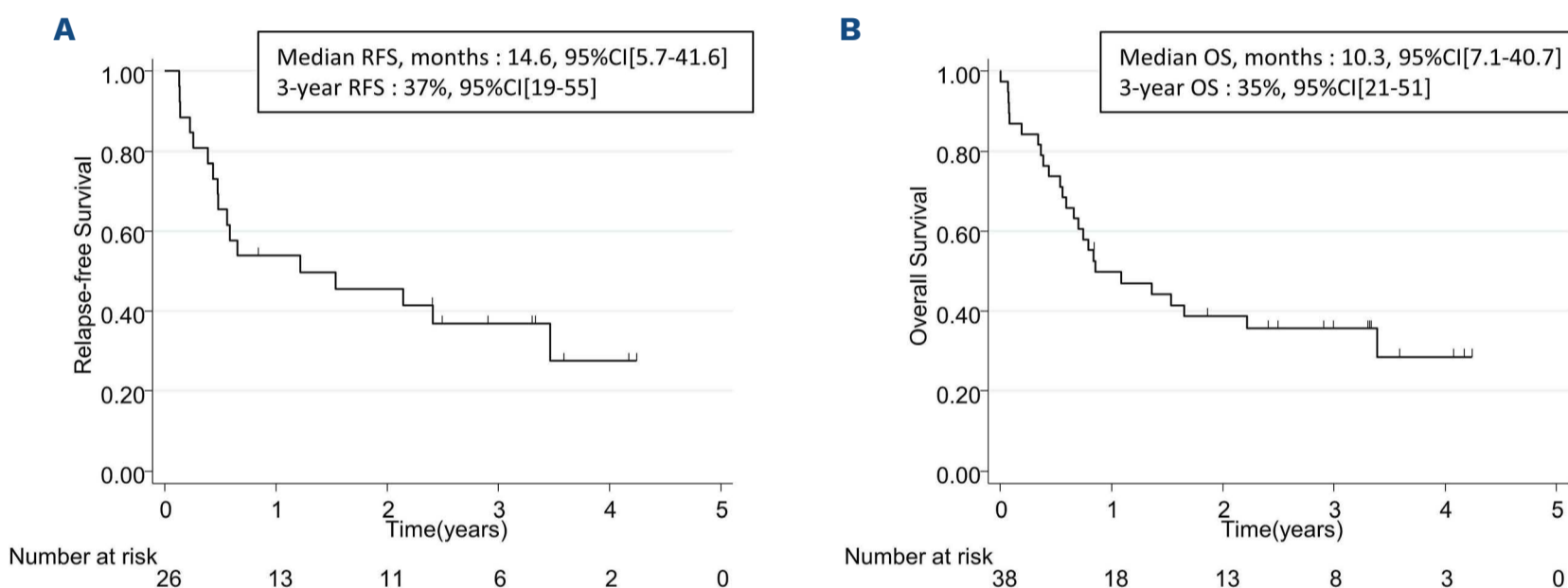
Table 2. Patient early response and late outcome.

	All N=73	MRD+ cohort N=35	Relapse cohort N=38
Complete Remission, N (%)	61 (85)	35 (100)	26 (68)
MRD Complete response, N (%)	52/60 (87)	31/35 (89)	21/25 (84)
Allo-HSCT in CCR, N (%)	35/61 (58)	23/35 (66)	12/26 (46)
Follow-up, median years (95% CI)	3.5 (3.1-3.7)	3.6 (3.1-3.8]	3.3 (2.5- 4.1)
RFS, median months (95% CI)	NR (14.9-NR)	NR (33.2-NR)	14.6 (5.7-41.6)
3y-RFS, % (95% CI)	45% (33-56)	65% (47-78)	37% (19-55)
OS, median months [95% CI]	40.7 (13.8-NR)	NR (NR-NR)	10.3 (7.1-40.7)
3y-OS, % (95% CI)	52% (39-62)	68% (50-81)	35% (21-51)

Allo-HSCT: allogeneic hematopoietic stem cell transplantation; CCR: continuous complete remission; MRD: minimal residual disease; PFS: progression-free survival (MRD+); RFS: relapse-free survival (REL); OS: overall survival; 95% CI: 95% confidence interval.

A

Median PFS, months : NR, 95%CI[33.2-NR]
3-year PFS : 65%, 95%CI[47-78]

Number at risk
35 26 25 19 4 1

B

Median OS, months : NR, 95%CI[NR-NR]
3-year OS : 68%, 95%CI[50-81]

Number at risk
35 28 26 20 4 1

Figure 2. Outcome of MRD+ patients. A) Relapse-free survival and (B) overall survival (OS) without censoring patients at allogeneic hematopoietic stem cell transplantation time. PFS: progression-free survival; CI: confidence interval; NR: not reached.

A

Median RFS, months : 14.6, 95%CI[5.7-41.6]
3-year RFS : 37%, 95%CI[19-55]

Number at risk
26 13 11 6 2 0

B

Median OS, months : 10.3, 95%CI[7.1-40.7]
3-year OS : 35%, 95%CI[21-51]

Number at risk
38 18 13 8 3 0

Figure 3. Outcome of relapsed patients. (A) Relapse-free survival and (B) overall survival (OS) without censoring patients at allogeneic hematopoietic stem cell transplantation time. CI: confidence interval.

We further investigated the prognostic impact of pre-blinatumomab tumor load in the relapse cohort. In the whole cohort, regardless of the treatment line, patients who received blinatumomab in CR2+ had similar characteristics (*Online Supplementary Table S2*) and a better outcome as compared to patients treated in overt relapse. Indeed, 3-year RFS and OS for patients in CR2+ at the time of blinatumomab were 59% and 66% respectively *versus* ≤9% (not evaluable, *P*=0.033) and 16% (*P*=0.003) respectively for patients in overt relapse (Figure 3C and D). Median RFS and OS were respectively 41.6 months and not reached in CR2+ patients, *versus* 6.7 months and 8.9 months respectively in patients with overt relapse at time of blinatumomab initiation. A multivariate analysis considering age, high-risk cytogenetics, number of prior relapses, allogeneic HSCT, and CR status at blinatumomab showed significantly shorter OS and RFS associated with CR status at blinatumomab and more advanced disease (Table 3).

A similar analysis performed in patients in first relapse showed the same advantage for patients exposed to blinatumomab in second CR after chemotherapy compared to patients who received blinatumomab in overt first hematological relapse. The 3-year RFS and OS for patients in second CR were 70% (median OS not reached) and 80% (n=10) respectively *versus* ≤11% (not evaluable, *P*=0.067) and 27% (*P*=0.025) in first hematological relapse (*Online Supplementary Figure S3*).

Discussion

This retrospective, multicenter study reports the outcome of 73 adult patients treated with blinatumomab for MRD+ or relapsed BCP-ALL within the French compassionate use program. Patient outcomes, CR and MRD response rates after blinatumomab were similar to those observed in
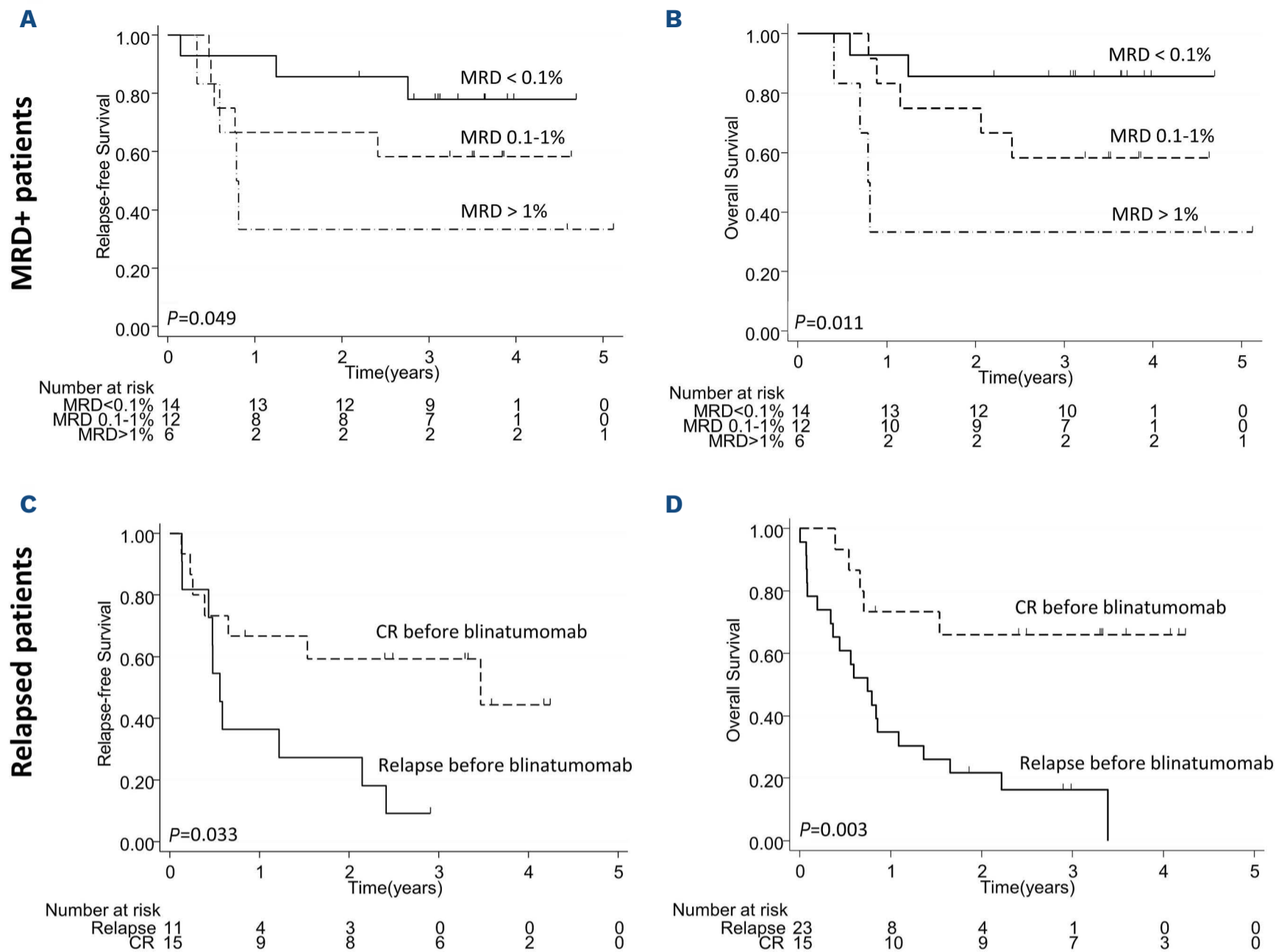
Figure 4. Impact of pre-blinatumomab tumor burden on outcome. (A) Relapse-free surviavl (RFS) and (B) overall survival (OS) in minimal residual disease-postive (MRD+) patients according to pre-blinatumomab MRD. (C) RFS and (D) OS in relapsed patients according to pre-blinatumomab complete response (CR).

larger prospective trials.[9,10] In addition, we report here that the tumor load before blinatumomab initiation has a strong impact on patient outcome whatever the disease status. This parameter should thus be considered to design future salvage strategies.

Among the patients exposed to blinatumomab in first CR and with persistent MRD, 89% achieved a complete MRD response. The median RFS and OS were not reached with a 3-year RFS and OS of 65% and 68% respectively. This observation is in line with the BLAST trial for adults with MRD+ ALL that reported a 80% complete MRD response rate after one course of blinatumomab.[10] In the BLAST subgroup analysis, patients in CR1 achieved a complete MRD response in 83% of cases after the first course of blinatumomab and the median RFS was not reached for patients who achieved complete MRD response. In the present cohort, censoring outcome analyses at the time of HSCT did not modify estimates, which should encourage to further investigate the role of transplantation in MRD+ patients after

blinatumomab therapy. Of note, heterogeneity in the techniques used to assess MRD response may be considered as a limitation of the present study.

Whereas the prognostic impact of MRD response after blinatumomab is well described,[10] the role of pre-blinatumomab MRD remains poorly explored. In the BLAST study, which included patients with MRD ≥0.1%, a complete MRD response was achieved in only six of nine (67%) patients with an MRD level ≥10%.[10] In the present MRD+ cohort, pre-blinatumomab MRD levels had a strong impact on patient outcome and inversely correlated with RFS and OS. In previous pediatric and adult ALL studies, the same impact was observed for pre-transplant MRD identified as a post-transplant relapse predictor.[16,17] In both pre-blinatumomab or pre-transplant settings, it remains unclear whether a high MRD level is just a marker of higher intrinsic resistance of the disease, or also contributes to unfavorable target-to-effector ratios that disable effector cells. In MRD+ patients, there are limited options in terms of

Table 3. Multivariate analysis for relapse-free survival and overall survival in minimal residual disease-positive and relapse cohorts.

	MRD+ cohort						Relapse cohort					
	RFS			OS			RFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age*	0.99	(0.96-1.04)	0.99	1.00	(0.96-1.05)	0.97	0.98	(0.95-1.01)	0.17	0.98	(0.95-1.01)	0.24
White blood cell count*	1.00	(0.99-1.00)	0.40	1.00	(0.99-1.00)	0.28	NA	NA	NA	NA	NA	NA
High-risk cytogenetics**	3.09	(0.56-17.0)	0.19	6.83	(0.86-53.99)	0.07	1.08	(0.48-2.39)	0.86	1.70	(0.69-4.19)	0.25
Number of prior relapses*	NA	NA	NA	NA	NA	NA	1.85	(1.10-3.12)	0.02	5.23	(2.56-10.72)	<0.001
Prior allo-HSCT	NA	NA	NA	NA	NA	NA	0.84	(0.37-1.95)	0.69	0.55	(0.19-1.63)	0.28
MRD at blinatumomab***	3.00	(1.15-7.84)	0.03	5.41	(1.67-17.44)	0.005	NA	NA	NA	NA	NA	NA
CR at blin *vs.* overt relapse	NA	NA	NA	NA	NA	NA	0.13	(0.04-0.37)	<0.001	0.07	(0.02-0.25)	<0.001

NA:not applicable; HR: hazard ratio; CI: confidence interval; blin: blinatumomab; RFS: replase-free survival; MRD: minimal residual disease. *continous variables **defined by either t(9;22)/*BCR-ABL1, KMT2A-r*, t(1;19)/*TCF3-PBX1*, or low hyploidy/near triploidy. *** 3-class MRD levels (<0.1%, 0.1-1%, >1%). allo-HSCT: allogeneic hematopoietic stem cell transplantation.

pre-blinatumomab intervention to reduce MRD levels. Pre-blinatumomab MRD level should thus remain a warning to guide further intervention.

In R/R patients, blinatumomab is approved as a single agent based on the results of two studies including the phase III TOWER study which demonstrated a superiority of blinatumomab on standard of care in terms of overall response rate and OS.[9] Whether blinatumomab should be used in fully relapsed patients or after a tumor burden reduction remains a matter of debate with a lack of controlled study addressing this question. In the TOWER study, 44% of R/R patients achieved a CR at 12 weeks, with 76% of MRD negativity among responders and a median OS of 7.7 months.[18] In patients with full relapse at the time of blinatumomab, we report very similar results with a CR rate of 48%, 82% of responders achieving a complete MRD response, and a median OS of 8.9 months. Interestingly, the outcome of the 15 relapsed patients who were exposed to blinatumomab in CR2+ was significantly better than those of relapsed patients exposed to blinatumomab in overt relapse (Figure 4C and D). There are obvious limitations to this non-controlled comparison including the fact that relapsed patients who achieved CR prior to blinatumomab exposure were by definition good responders at relapse, achieving a new CR having been described as one of the most important prognostic factor after relapse.[19,20] However, the difference in RFS between patients in CR before blinatumomab exposure (n=15) and patients achieving CR after blinatumomab (n=11) also suggests that,

despite similar MRD responses, the advantage of having reached a CR after chemotherapy *versus* blinatumomab still persists after CR (Figure 4C; Table 3). Thus, the prognostic value of a negative MRD after blinatumomab differs depending on disease status before blinatumomab. Combined with CR status at blinatumomab, it could have many implications in terms of relapse prevention strategies post blinatumomab. Of note, the prognostic impact of pre-therapeutic tumor burden was also pointed out with CAR-T cell therapy.[21] After tisagenlecleucel, it was suggested that a high tumor burden was associated with a higher risk of CD19-negative relapse and escape to CAR-T surveillance. In the present study, we were not able to collect the CD19 status of leukemic cells at relapse. Given that CD19-negative relapse after blinatumomab was reported in up to one third of patients, further studies should investigate whether the risk of CD19 antigen loss does correlate with tumor burden at the time of treatment.[22] Recently, the use of blinatumomab in second CR was strongly supported by two different randomized studies conducted in children and young adults with first intermediate- or high-risk disease. In the study by Locatelli *et al.*,[23] the 36-month OS was 81.1% after blinatumomab consolidation *versus* 55.8% after chemotherapy-based consolidation. In the study by Brown *et al.*,[24] the 24-month OS was 71.3% after blinatumomab consolidation and 58.4% after chemotherapy. Interestingly, in the present study, the 3-year OS of the few patients (n=10) who received blinatumomab in second CR was 80%. In adult Ph-negative

BCP-ALL aged up to 60 years old, a second CR is expected in about 50% of cases.[19,20] The most important factor associated with the chance to reach a second CR is CR1 duration. In late relapses with CR1 duration >18 months, reported CR2 rates ranged from 58% to 68%.[19,20] In the TOWER study for adult R/R B-ALL, patients in first relapse could be included if CR1 duration was shorter than 12 months or after HSCT. Patients who received blinatumomab as first salvage, most of them being in first relapse, had an overall response rate of 51%, a CR rate of 44%, and a median survival of 11.1 months.[25] Altogether, these observations encourage to try to reach a second CR with chemotherapy-based regimen before exposing patients to blinatumomab consolidation, particularly in younger patients with late relapse.

The place of blinatumomab combined to chemotherapy in frontline or R/R B-ALL is being intensively explored. The MD Anderson Cancer Center reported on the combination of Hyper-CVAD-derived regimen, inotuzumab ozogamicin, and blinatumomab in elderly patients with frontline B-ALL or in younger adult patients with R/R diseases.[26,27] More recently, phase II assessing the role of frontline consolidation with blinatumomab in adult B-ALL were reported by the GIMEMA group and by our group.[28,29]

In conclusion, this real-world study confirms the benefit of blinatumomab in adult patients with either primary resistant BCP-ALL or at relapse and suggests an impact of pre-blinatumomab tumor burden on patient outcome. Many limitations have been highlighted throughout the discussion, mostly related to the retrospective nature of the study, to the non-controlled nature of the comparisons, and more specifically to the selection of patients in second CR after chemotherapy compared to patients exposed to blinatumomab in overt relapse. It is however unlikely that a randomized study will address this important question. In early resistant disease with MRD+, our observation supports the design of post-blinatumomab strategies including transplantation. In relapsed patients, especially in first salvage, our results along with recent published observations support to discuss the best timing schedule of blinatumomab, after salvage chemotherapy rather than in overt relapse. The underlying mechanisms that contribute to an increased risk of failure in patients with high tumor burden remain to be explored.

Data-sharing statement
For original data, please contact nicolas.boissel@aphp.fr

References

1. Dombret H, Cluzeau T, Huguet F, Boissel N. Pediatric-like therapy for adults with ALL. Curr Hematol Malig Rep. 2014;9(2):158-164.
2. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol. 2009;27(6):911-918.
3. Huguet F, Chevret S, Leguay T, et al. Intensified therapy of acute lymphoblastic leukemia in adults: report of the randomized GRAALL-2005 clinical trial. J Clin Oncol. 2018;36(24):2514-2523.
4. Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. Blood. 2014;123(24):3739-3749.
5. Dhédin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood. 2015;125(16):2486-2496; quiz 2586.
6. Tanguy-Schmidt A, Rousselot P, Chalandon Y, et al. Long-term follow-up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. Biol Blood Marrow Transplant. 2013;19(1):150-155.
7. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711-3719.
8. Desjonquères A, Chevallier P, Thomas X, et al. Acute lymphoblastic leukemia relapsing after first-line pediatric-inspired therapy: a retrospective GRAALL study. Blood Cancer J. 2016;6(12):e504.
9. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376(9):836-847.
10. 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.
11. Martinelli G, Boissel N, Chevallier P, et al. Complete hematologic and molecular response in adult patients with

relapsed/refractory Philadelphia chromosome–positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. J Clin Oncol. 2017;35(16):1795-1802.

12. Boissel N. ALL in escape room. Blood. 2021;137(4):432-434.

13. Zhao Y, Aldoss I, Qu C, et al. Tumor-intrinsic and -extrinsic determinants of response to blinatumomab in adults with B-ALL. Blood. 2021;137(4):471-484.

14. Duell J, Dittrich M, Bedke T, et al. Frequency of regulatory T cells determines the outcome of the T-cell-engaging antibody blinatumomab in patients with B-precursor ALL. Leukemia. 2017;31(10):2181-2190.

15. Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711-3719.

16. Bader P, Kreyenberg H, Henze GHR, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol. 2009;27(3):377-384.

17. Logan AC, Vashi N, Faham M, et al. Immunoglobulin and T cell receptor gene high-throughput sequencing quantifies minimal residual disease in acute lymphoblastic leukemia and predicts post-transplantation relapse and survival. Biol Blood Marrow Transplant. 2014;20(9):1307-1313.

18. Kantarjian H, Stein A, Gökbuget N, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376(9):836-847.

19. Gökbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood. 2012;120(10):2032-2041.

20. Desjonquères A, Chevallier P, Thomas X, et al. Acute lymphoblastic leukemia relapsing after first-line pediatric-inspired therapy: a retrospective GRAALL study. Blood Cancer J. 2016;6(12):e504.

21. Dourthe M-E, Rabian F, Yakouben K, et al. Determinants of CD19-positive vs CD19-negative relapse after tisagenlecleucel for B-cell acute lymphoblastic leukemia. Leukemia. 2021;35(12):3383-3393.

22. Pillai V, Muralidharan K, Meng W, et al. CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior blinatumomab therapy. Blood Adv. 2019;3(22):3539-3549.

23. 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.

24. Brown PA, Ji L, Xu X, et al. Effect of postreduction 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.

25. Dombret H, Topp MS, Schuh AC, et al. Blinatumomab versus chemotherapy in first salvage or in later salvage for B-cell precursor acute lymphoblastic leukemia. Leuk Lymphoma. 2019;60(9):2214-2222.

26. Jabbour EJ, Sasaki K, Ravandi F, et al. Inotuzumab ozogamicin in combination with low-intensity chemotherapy (mini-HCVD) with or without blinatumomab versus standard intensive chemotherapy (HCVAD) as frontline therapy for older patients with Philadelphia chromosome-negative acute lymphoblastic leukemia: a propensity score analysis. Cancer. 2019;125(15):2579-2586.

27. Jabbour E, Sasaki K, Short NJ, et al. Long-term follow-up of salvage therapy using a combination of inotuzumab ozogamicin and mini-hyper-CVD with or without blinatumomab in relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia. Cancer. 2021;127(12):2025-2038.

28. Bassan R, Chiaretti S, Della Starza I, et al. Preliminary results of the GIMEMA LAL2317 sequential chemotherapy-blinatumomab front-line trial for newly diagnosed adult Ph-negative B-lineage ALL patients. Hemasphere. 2021;5(S2):8.

29. Boissel N, Huguet F, Graux C, et al. Frontline consolidation with blinatumomab for high-risk philadelphia-negative acute lymphoblastic adult patients. Early results from the Graall-2014-QUEST phase 2. Blood. 2021;138(Suppl 1):S1232.