Published in final edited form as:

Leuk Lymphoma. 2020 January ; 61(1): 7–17. doi:10.1080/10428194.2019.1641802.

Immunotherapeutic options for management of relapsed or refractory B-cell acute lymphoblastic leukemia: How to select newly approved agents?

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Abstract

Recently, immunotherapeutic agents such as inotuzumab ozogamicin (INO), blinatumomab (BLIN), and tisagenlecleucel (TISA) have been approved for treatment of relapsed or refractory (R/R) acute lymphoblastic leukemia (ALL). No head to head trials have compared these agents. Thus, various factors influence the decision to choose an appropriate treatment for R/R ALL. INO may be preferred in patients with high tumor burden; BLIN is preferred in patients with low tumor burden or to eradicate minimal residual disease (MRD). Both INO and BLIN, compared to standard chemotherapy, increase the probability of receiving subsequent hematopoietic stem cell transplant (HSCT). TISA, approved for patients ≥ 25 years of age, is effective regardless of tumor burden or prior receipt of HSCT and can be used as a definite treatment in some patients. Further studies comparing the efficacy, safety, and other outcomes related to different immunotherapeutic options in combination with other treatment modalities and among themselves are needed.

Keywords

relapsed/ refractory acute lymphoblastic leukemia; Inotuzumab ozogamicin; Blinatumomab; Tisagenlecleucel; immunotherapy

Introduction

The use of multiagent chemotherapy in patients with Philadelphia chromosome (Ph) negative (Ph-) B-cell acute lymphoblastic leukemia (ALL) leads to complete remission (CR) in more than 80% of patients [1]. About 50% of the newly diagnosed patients may achieve long-term disease control with further consolidation and maintenance but 10% of patients

have primary refractory disease [2, 3]. Additionally, many patients with ALL will relapse subsequently after attaining remission with initial chemotherapy [4, 5]. Relapsed or refractory (R/R) B ALL confer a poor prognosis and previously had limited treatment options [4, 5]. Only 20–30% of these patients achieve second CR with standard salvage chemotherapy [6]. In 2017, the Food and Drug Administration (FDA) approved Inotuzumab ozogamicin (INO) and Blinatumomab (BLIN) for therapy of Ph+ or Ph- R/R ALL based on large randomized trials (Table 1) [7, 8]. INO is a humanized anti-CD22 IgG4 monoclonal antibody bound to calicheamicin [9]. B-cell ALL blasts express CD22, making them an excellent target for INO [10]. Similarly, BLIN is a bispecific T-cell engager antibody construct that allows cytotoxic T-cells to recognize and eliminate CD19-expressing B cells [11]. Tisagenlecleucel (TISA, formally CTL09), is a CD19 directed chimeric antigen receptor (CAR) T-cell therapy that was approved in May 2018 for patients with refractory ALL or those with second relapses or beyond [12]. Here we discuss about new immunotherapeutic drugs and therapy selection for R/R ALL.

Choice of therapy

INO, BLIN and TISA are preferred over traditional chemotherapy regimens for R/R ALL, however, trials comparing different immunotherapeutic options have not been conducted. Table 1 depicts the pivotal trials leading to approval of these immunotherapeutic agents and differences in the study population included in these trials. Compared to INO, which was used as a 1st or 2nd salvage treatment in adult patients with Philadelphia chromosome (Ph) + or Ph- R/R ALL, BLIN was used in more heavily pretreated patients including those with 2nd or greater relapse [13, 14]. In TISA trials, patients were 3–21 years of age who relapsed after multiple salvage treatments with or without prior use of HSCT. [15].

There are no head to head trials comparing INO, BLIN, or TISA with each other. One study used the results from INO-VATE ALL trial and TOWER trial to make indirect comparison of the relative efficacy of INO versus BLIN [16]. Methods such as network meta-analysis, matching-adjusted indirect comparison or simulated treatment comparison were used to produce less biased estimates. Simulated treatment comparison showed that INO, compared to BLIN, had significantly better remission and HSCT rate but similar EFS and OS. However, another study showed potential survival benefit with BLIN compared to INO [17]. Thus, the choice of the immunotherapeutic options depends on several factors including expression or loss of CD19 or CD22 receptors in B-cells, age of patients, disease burden, and anticipated adverse effects (Figure 1). INO is effective regardless of age but grade 3 adverse effects are more likely in patients >55 years of age [13]. BLIN can induce good responses in older patients or those with multiple comorbidities but adverse events may be less tolerated in older adults [18, 19, 20]. TISA is approved for pediatric and younger adults up to 25 years of age with refractory ALL or 2nd or more relapse; however, ongoing CAR T-cell trials allow older adults as well [12]. Patients with high disease burden may get a higher benefit with INO. A subgroup analysis of the INO-VATE trial demonstrated that INO had better rates of CR or CR with incomplete hematologic response (CRi) and minimal residual disease (MRD) negativity compared to standard chemotherapy regardless of disease burden [13, 21]. BLIN is better in low tumor burden disease with excellent responses in MRD positive (MRD+ve) cases [20]. In one study, patients with <50% blasts in bone marrow had

better CR/CRi rates compared to those with >50% of blasts (73% vs 29%) [20]. Toxicities related to BLIN is also higher among patients with higher tumor-burden [22]. BLIN use was associated with grade 3 adverse events in 16% of patients with MRD+ve disease compared to 87% of patients with higher tumor burden [14, 23]. TISA is effective regardless of disease burden. However, higher tumor burden may correlate with more serious cytokine release syndrome (CRS) [24, 25].

All immunotherapeutic agents have unique adverse effects which are uncommon but can be severe and life-threatening. INO may lead to veno-occlusive disease (VOD), especially in patients subsequently undergoing HSCT [13, 26]. The use of INO in first relapse, limiting INO to 2 cycles before HSCT, weekly dosing, and possibly the use of drugs such as ursodeoxycholic acid and defibrotide may decrease the risk of VOD [26, 27, 28, 29]. Lower dose INO is currently being studied in clinical trials with aims to reduce the risk of toxicities such as VOD while maintaining high response rate ([NCT03094611](#), [NCT03677596](#)).

Important adverse effects associated with BLIN and TISA include CRS and neurotoxicity; incidence of these adverse effects is higher with TISA [8, 15, 22, 30]. Stepwise dosing of BLIN and premedication with steroids reduces the risk of CRS [20, 31]. Tocilizumab, an anti-interleukin-6 receptor, with or without corticosteroids can be used for treatment of CRS with TISA [12]. Both BLIN and TISA are considered contraindicated in patients with neurological disorders, although a recent study demonstrates preliminary safety of BLIN in this setting [15, 32, 33, 34].

INO can be given as an outpatient with weekly doses. BLIN is a continuous infusion and requires patient to be admitted to hospital in the beginning. TISA is given as a single infusion in the inpatient setting. The necessity of hospitalization should be considered while deciding between these options. In contrast to INO and BLIN which can be initiated immediately, TISA needs a few weeks for production and administration to the patients. This means most R/R patients need additional therapy while they are prepared for TISA or other CAR T-cell therapy. Subsequent treatment plans may also determine the choice of therapy. INO or BLIN are often used as a bridge to HSCT in patients desiring curative intent therapy. Patients preferring to avoid HSCT may be better served with CAR T-cell therapy.

Additionally, if there is a high possibility to undergo CAR T-cell therapy in the future, there is a small risk of loss of CD19 expression with BLIN. Changes in CD19 expression, among other factors, have been implicated in failure of BLIN and CAR-T cell therapy [35, 36, 37, 38, 39, 40, 41]. Similarly, loss of CD22 expression may lead to INO failure [29, 42]. Different factors associated with failure of these immunotherapeutic agents and subsequent choice of therapy are listed in table 2 [35, 43, 44, 45, 46, 47, 48, 49].

Since VOD was reported in 11% of patients in the INO-VATE trial, some studies have used lower fractionated doses of INO with low intensity chemotherapy such as mini-HCVD, to decrease the risk of VOD [50, 51]. Mini-HCVD, modified from standard hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) regimen, lacks doxorubicin and contains reduced doses of cyclophosphamide, dexamethasone, methotrexate and cytarabine. Jabbour et al. reported use of lower doses of INO with mini-HCVD, with or without BLIN for up to 4 cycles after the completion of INO [51]. Weekly lower dose

schedule of INO, compared to a single higher loading dose every month, was safe and equally effective. INO was given as 2 weekly fractionated doses- a total of 0.9mg/m² during cycle 1 and 0.6 mg/m² on cycles 2, 3, and 4. Preliminary results are encouraging. Two-year OS was 54%, and 50% of total patients underwent HSCT. VOD was reported in 10% of patients and all cases were grade 3/4 in severity. Weekly lower doses had lower clearance rate and better area under the curve, however, still had high rate of VOD. In a phase II trial, the combination of INO mini-HCVD, as a first salvage therapy, resulted in 1-year OS of 57%; VOD was seen in 15% of patients [50]. However, given a single-center study with relatively small sample size and a lack of substantial reduction in the risk of VOD, further evidence is needed before routinely using INO-chemotherapy over single-agent INO outside of clinical trials. Lower dose INO is currently being studied in clinical trials with aims to reduce the risk of toxicities such as VOD while maintaining high response rate ([NCT03094611](#), [NCT03677596](#)).

Ph- R/R ALL in transplant eligible patients

The initial approach to R/R ALL depends primarily on whether the patient is potential candidate for HSCT. In transplant eligible patients, early referral to a transplant center for pre-transplant evaluation and donor search is important. Since status of disease before HSCT correlates with outcome, attaining complete remission, preferably MRD negativity is the goal. INO and BLIN are both excellent options for transplant-eligible patients. In the pivotal trials, 41% and 24% of patients treated with INO and BLIN were able to proceed to HSCT [13, 14, 16, 26, 52, 53, 54]. In transplant eligible patients, INO may increase the risk of VOD with increased mortality in patients receiving HSCT [13, 26]. For this reason, the use of INO should be limited to 2 cycles, and conditioning regimens containing dual alkylating agents, thiopeta, or both should be avoided. However, limiting INO to 2 cycles may not be necessary with lower fractionated doses of INO [51]. Expert panel recommendations also suggest to use ursodiol and avoid hepatotoxic agents (e.g., azoles) in combination with high-dose alkylator-conditioning regimen [27].

Ph- R/R ALL in transplant ineligible patients

Although HSCT is the only potentially curative modality for any ALL patient, immunotherapeutic options for R/R cases may offer a chance of longer-term disease control without HSCT in selected patients. Transplant ineligible patients may include older patients, those with multiple comorbidities, or decreased performance status. INO can be an effective option in transplant ineligible patients. With a lower risk of VOD without HSCT, INO may be used for a total of 6 cycles. INO, which can be used in outpatient setting, may be especially attractive in transplant ineligible patients who desire to avoid hospitalization. BLIN is also effective in transplant ineligible patients, and a small proportion of patients may achieve long-term disease control without HSCT. MRD negative status, T-cell expansion and B cell depletion are associated with longer survival [55].

Post-HSCT relapse

The rate of relapse in ALL after HSCT is reported to be 26–64% [56, 57, 58, 59]. The INO-VATE trial included 17 patients with prior use of HSCT [13]. INO resulted in CR in 76% of those patients. Other studies have also reported use of INO in small number of patients who relapse after HSCT [16, 28, 42]. An ongoing phase I/II study will determine the safety of INO maintenance after HSCT ([NCT03104491](#)).

The TOWER study included 94 patients with a history of previous HSCT; remission rate (complete or partial) was 40% with median survival of 7.7 months in those patients [14]. In another study, the use of BLIN in patients who relapsed after HSCT was associated with a CR/CRi rate of 45% with BLIN. The remission rate was similar to HSCT-naïve patients [20]. For the patients with prior HSCT, 31% of responders subsequently underwent another HSCT, and median OS was 8.4 months [20]. BLIN is currently being studied as post-transplant maintenance in a phase II trial ([NCT02807883](#)).

Patients with MRD+ve disease

MRD is an important prognostic factor for frank disease relapse and OS, hence clearance of MRD is of vital importance. BLIN was initially used in patients with MRD+ve disease after first standard chemotherapy and has consistently shown excellent results. The rates of CR achieved with BLIN is much higher in patients with MRD than patients with high tumor burden [20, 37]. In a phase II trial of patients with MRD+ve disease [23], MRD negativity ($<10^{-4}$ after one cycle) was seen in 88% of patients. The use of BLIN resulted in a median OS of 36 months and a plateau in OS after about 3 years; however, the number of patients was low. A subsequent study of 36 patients reported a median OS of 13 months with MRD clearance following the use of BLIN; 28% of all patients survived beyond 30 months [55]. Based on these data and favorable safety profile in this specific population, BLIN is the current preferred option for management of MRD+ve patients both as a definite treatment as well as pre-HSCT therapy. BLIN is the only agent currently approved for MRD+ve disease. Patients who achieve MRD negativity after BLIN should be assessed for potential HSCT considering both risks and benefits of HSCT versus BLIN alone. While HSCT is considered by many for young fit patients who achieve MRD negativity, some patients may achieve long term disease control with BLIN alone. However, the type of patients who may not need HSCT and may achieve long term disease control with BLIN alone is unknown. Gökbuget et al. reported that patients who achieve MRD negativity after 1 cycle of BLIN may not need subsequent HSCT [23]. Survival was significantly worse in non-transplant cases compared to transplant cases who achieved MRD negativity after more than 1 cycle. Select group of patients such as older less-fit patients, those with multiple comorbidities, who do not desire HSCT and have MRD after one cycle of BLIN may receive BLIN alone.

The use of INO is expected to achieve high responses in MRD+ve patients, however, data for this specific population is not available yet. In the INO-VATE trial, 78% of patients in INO group had undetectable MRD (defined as $<0.01\%$ marrow blasts) compared to 38% with standard chemotherapy. Other studies have also reported high rates of MRD clearance

with the use of INO [13, 16, 26, 52]. A phase II trial is enrolling patients with MRD to determine efficacy of INO in this setting ([NCT03441061](#)).

R/R Ph+ B-cell ALL

Patients with R/R Ph+ ALL can be treated with newer generation of tyrosine kinase inhibitors (TKIs), BLIN, INO or CAR T-cells. Among patients who fail imatinib and standard chemotherapy, dasatinib with chemotherapy may be effective as it is active against most BCR-ABL1 kinase domain mutations [60, 61]. However, dasatinib, similar to imatinib, is ineffective against BCR-ABL T315I substitution [62]. Ponatinib is highly effective against BCR-ABL T315I mutation and is approved for patients with BCR-ABL T315I mutation [63]. In one study, ponatinib induced major hematological response and major cytogenetic response in 36% and 32% of patients respectively; 100% major hematological response was reported against the patients with BCR-ABL T315I mutation [64]. In a phase II trial (n=37), ponatinib in combination with hyper-CVAD resulted in a 2-year EFS of 81% [65].

BLIN overcomes T315I mutation-induced resistance resulting in immune-mediated death of Ph+ blasts, making HSCT a viable option after relapse. In the ALCANTRA phase II trial of 45 patients previously treated with TKIs, the use of BLIN was associated with CR or CR with partial hematologic recovery in 36% patients: 87% had MRD negativity and 44% underwent subsequent HSCT [66]. Median OS was 7.1 months. Out of 22% of total patients with T315I mutation, 40% achieved CR or CR with partial hematologic recovery and MRD negativity. A retrospective study of 12 patients reported use of BLIN in combination with TKI resulting in CR of 50% and 1-year OS of 73% [67]. In another study of 6 patients where BLIN was used with a TKI (dasatinib, imatinib, ponatinib), 33% received HSCT while 50% were awaiting HSCT at the time of publication [68]. Given preliminary safety data and the possibility that combination therapy may maximize disease control, as an off-label use in clinical practice, BLIN is often combined with TKI in R/R Ph+ ALL. The choice of TKI depends on the TKI used as a part of upfront therapy and the presence of any mutations that may confer resistance to certain TKIs. Ponatinib, if not used earlier, is often preferred given its potency. BLIN as a single agent is effective in patients who have failed ponatinib.

Although a dedicated study has not been conducted to our knowledge, INO trials allowed Ph + R/R ALL. Out of 38 Ph+ patients from the INO-VATE trial and a phase I/II trial who failed prior TKI ± HSCT, 66% achieved complete remission, and 63% had MRD negativity [13, 52, 69]. Median OS was 8 months, and 31% of patients underwent subsequent HSCT. An ongoing phase I/II trial is studying the combination of INO with a TKI (bosutinib) for patients with R/R Ph+ ALL ([NCT02311998](#)). In an interim report, 14 patients were treated with a combination of bosutinib and INO: 78% achieved a CR and 57% achieved MRD negativity by flow cytometry [70].

Tisagenlecleucel or CAR T-cell therapy

TISA is the first gene therapy approved for treatment of patients 25 years who have refractory ALL or 2 relapses [15, 71]. In the global phase II ELIANA trial (n=75), CR/CRi was reported in 81% patients within 3 months; all patients with remission achieved MRD

negativity [15]. An updated analysis demonstrated a RFS of 66% and an OS of 70% at 18 months with a plateau in RFS curve starting at about 10 months [72]. It should be noted that among the total patients (n=92) enrolled in the trial, CR/CRi rate was 66%, and 7 patients died before TISA therapy. In the ELIANA trial, grade 3 adverse effects related to TISA were reported in 73% of patients [15]. The most important adverse effects such as CRS and neurological events were reported in 77% and 40% of patients respectively. In half of the patients with CRS, tocilizumab was used for treatment. Neurological events commonly occurred during or after resolution of CRS. Severe neurological events were reported more frequently in patients with higher grade CRS.

At the present time, TISA can be used as a definite treatment without subsequent use of HSCT in patients who achieve and maintain MRD negative status after treatment [39, 47, 73]. Sustained B-cell aplasia has also been recommended as another tool to decide against HSCT [39].

It is interesting to note that other CAR T-cell product has been used as a bridge to another HSCT in some patients who relapsed after previous transplant. Lee et al., in a trial conducted at National Institutes of Health Clinical Center, studied 51 patients with R/R ALL in which 61% achieved CR; 90% of patients with CR were MRD negative [74]. MRD-ve patients who underwent HSCT had lower relapse rate and longer leukemia free survival than those who did not undergo HSCT. Patients with more than 5% blasts before treatment have better results HSCT after CAR T-cell therapy [75].

In a phase I/IIA study, 30 heavily pretreated patients including BLIN use and prior HSCT were treated with TISA: CR was achieved in 90% of patients and OS at 6 months was 78% [39]. Similar results were obtained with another phase I/IIA study of 59 patients out of which 2/3rd had prior HSCT [24]. CAR T-cell therapy has better rates of remission and EFS than INO or BLIN in cases of ALL relapse after HSCT [76].

Conclusion and future directions

Immunotherapeutic agents such as INO, BLIN and TISA are preferred over traditional chemotherapy regimens for R/R ALL. Better quality of life has been reported with INO, BLIN and TISA in comparison to standard chemotherapy [13, 14, 34, 45, 77]. However, there are no efficacy, safety, quality of life or cost-effectiveness studies comparing these agents. Choosing one of these agents for a patient with R/R ALL depends on several factors such as transplant eligibility, Ph chromosome positivity, loss or expression of CD19 or CD22 receptors in B-cells, disease burden, anticipated adverse effects, and prior treatment history (Figure 1). Future studies looking at the efficacy, safety, and other relevant outcomes such as quality of life related to immunotherapy alone or in comparison to other treatment options are underway (Table 3). A study comparing TISA ± chemotherapy with INO or BLIN ± chemotherapy is ongoing (NCT03628053). Additional studies combining immunotherapy with other types of treatment such as chemotherapy, radiation therapy and targeted therapies may be carried out [78]. With proven efficacy in R/R ALL, upfront use of immunotherapy such as INO, BLIN, or TISA are also being studied or planned.

One of other challenges is knowing how to optimally combine or sequence various treatment options over the course of treatment [79]. In some cases, combination of immunotherapy agents that have certain unique properties can be helpful. For instance, patients achieving MRD+ve disease with INO might benefit from subsequent BLIN to attain remission. TISA can increase the duration of remission after use of INO, or BLIN, or both. Since patients may relapse with TISA via different mechanisms such as loss of B-cell aplasia and CD19 expression, HSCT can act as a consolidation therapy to maintain remission [80]. Use of CAR-T cell as a bridge to HSCT in ALL patients who have not undergone HSCT before relapse has shown promising results [81]. TISA may also be used as definite therapy, reserving HSCT in cases who relapse after TISA. However, it should be noted that patients who relapsed after HSCT but attained remission with TISA, 2nd HSCT may develop more treatment related toxicities and mortality.

Mechanisms of resistance and management of patients who fail immunotherapeutic agents remain important research questions. Since loss of CD19 expression is an important cause of resistance to BLIN and TISA, targeting other antigens such as CD22 can increase duration of remission. CAR-T cell therapy against CD22 antigen is reported to be effective in patients relapsing after CD19 directed CAR-T cell therapy [82]. Thus, CAR-T cell constructs which act against different targets, such as CD19 and CD22, and potentially decrease resistance or relapse are being assessed (NCT03330691, NCT03233854). CD22 CAR-T cell therapy may also be studied in patients who relapse or are refractory to BLIN [83]. Biomarker driven personalized cancer therapy to address the resistant mechanisms and develop targeted treatment options may potentially overcome current obstacles in the near future [84, 85].

Funding

This work was supported by the National Institute of General Medical Sciences, 1 U54 GM115458, which funds the Great Plains IDeA-CTR Network, and the Fred and Pamela Buffett Cancer Center Support Grant from the National Cancer Institute (P30 CA036727). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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research funding from Pfizer and Amgen and served as a consultant for Pfizer. E.V., K.L., R.A., J.B., A.D.L., and L.F. are employees and stockholders of Pfizer. H.M.K. has received research funding from Pfizer, Amgen, Astex, Novartis, and BMS. A.S.A. has received research funding and served as a consultant for Pfizer. A.S. declares no competing financial interests. eng.

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Figure 1: Choice of therapy for relapsed/refractory acute lymphoblastic leukemia

* Please refer to the ‘conclusion and future perspectives’ section in the manuscript for ongoing studies aimed at optimizing outcomes. While clinical trials are preferred, treatment options listed here are recommended for use outside of a clinical trial.

† INO and BLIN may act as a bridge to transplant, although both can be used as a single agent in patients unsuitable for transplant. INO and BLIN can be used as definite treatment for long term disease control.

‡ INO may be limited to 2 cycles in transplant eligible patients (as recommended by an expert panel) [28].

‖ BLIN may be used in patients who achieve MRD positive disease after INO use.

§ TISA is only approved for pediatric and younger adults up to 25 years of age with refractory ALL or 2nd or more relapse. TISA is considered a definite treatment without subsequent transplant in patients who achieve MRD negative CR and persistent B-cell aplasia. HSCT can be used as a consolidation therapy in some patients, particularly those not achieving MRD negative CR after TISA.

ALL- Acute lymphoblastic leukemia; Allo-HCT- Allogenic hematopoietic cell transplant; BLIN- Blinatumomab; INO- Inotuzumab ozogamicin; MRD- minimal residual disease; R/R- relapsed /refractory; TISA- Tisagenlecleucel

Table 1.

Pivotal studies for inotuzumab ozogamicin, blinatumomab, and tisagenlecleucel

	Inotuzumab ozogamicin [11]	Blinatumomab [12]	Tisagenlecleucel [13]
Target	Anti-CD22 antibody conjugated to calicheamicin	Bispecific monoclonal antibody, binds to CD3-positive T cells and CD19-positive B cells	Autologous T-cells with transgene encoding chimeric antigen receptor targeting CD19-positive B cells
Pivotal trial	INO-VATE ALL (Phase III)	TOWER (Phase III)	ELIANA (Phase II)
ClinicalTrials.gov number	NCT01564784	NCT02013167	NCT02435849
Number of patients studied	326 (218 used in primary analysis)	405 (376 received treatment)	92 (75 used in primary analysis)
Randomization	1:1	2:1	No
Comparison group	Salvage chemotherapy such as FLAG, cytarabine and mitoxantrone, high-dose cytarabine	Salvage chemotherapy such as FLAG with or without anthracycline, high-dose cytarabine, methotrexate and clofarabine-based regimens	None
Inclusion criteria	Exposure to 1–2 prior therapies	No limit to the number of prior therapies	Median 3 prior therapies (61% had HSCT)
Philadelphia chromosome positive ALL	Included (N=32)	Excluded but a separate study included this cohort of patients [†]	Included
CR [*]	80% vs. 29%	44% vs. 25%	81%
MRD negative status (among patients who achieved CR) [*]	78% vs. 28%	76% vs. 48%	100%, 95% by day 28
Duration of remission [*]	4.6 vs. 3.1 months	7.3 vs. 4.6 months	Not reached
Median PFS [*]	5.0 vs. 1.8 months	31% vs. 12% EFS at 6 months	73% at 6 months; 59% at 12 months
Median overall survival [*]	7.7 vs. 6.7 months	7.7 vs. 4.0 months	19.1 months
Overall survival [*]	23% vs. 10% at 2 years	54% vs. 39% at 6 months	90% at 6 months; 76% at 12 months
Receipt of HSCT [*]	41% vs. 11%	24% vs. 24%	10.67%
Grade 3 adverse events [*]	91% vs. 95%	87% vs. 92%	88%
Unique adverse events of the drug	Veno-occlusive liver disease (all grades, 11%)	Cytokine release syndrome (grade 3, 5%), neurologic event (grade 3, 9%)	Cytokine response syndrome (grade 3, 46.67%), neurologic events (grade 3, 13%)

CR- complete remission with or without hematologic recovery; EFS- event-free survival; FLAG- fludarabine, cytarabine and granulocyte colony-stimulating factor; HSCT-hematopoietic stem cell transplant; MRD- minimal residual disease; NA- Not applicable; PFS progression-free survival.

^{*} compared to the control group for inotuzumab ozogamicin and blinatumomab.

[†] A single-arm, multicenter study (ALCANTARA, [NCT02000427](#)) enrolled 45 patients with Philadelphia chromosome-positive ALL, who had disease resistance or intolerance to second generation tyrosine kinase inhibitors. Blinatumomab resulted in a complete remission with complete or partial hematological recovery in 36% with a median duration of remission of 6.7 months.[17]

Table 2:

Mechanisms of failure of immunotherapy and treatment options

	Mechanisms of failure	Treatment options outside of clinical trials
INO	<ul style="list-style-type: none"> • Loss of or decreased CD 22 expression • Translocation- t(4;11) 	<ul style="list-style-type: none"> • BLIN • CAR T-cell therapy • HSCT
BLIN	<ul style="list-style-type: none"> • Loss of or decreased CD19 expression • Acquired mutations • Alternative splicing of CD19 cells • Selection of CD19 clones • Myeloid switch 	<ul style="list-style-type: none"> • INO ± mini-HCVD • HSCT • CAR T-cell • Re-challenge with BLIN in the future can be effective in some patients
TISA	<ul style="list-style-type: none"> • Loss of or decreased CD19 expression • Lack of persistence and expansion of CAR T-cells in blood • Disrupted antigen trafficking • Antigen escape variants 	<ul style="list-style-type: none"> • Lymphodepletion with cytotoxic chemotherapy • INO • CD22 CAR T-cell therapy/novel strategies

BLIN- Blinatumomab; CAR- Chimeric antigen receptor; HSCT- Hematopoietic stem cell transplant; INO- Inotuzumab ozogamicin; mini-HCVD- mini-hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone); TISA- Tisagenlecleucel

Table 3:

Ongoing phase III trials for treatment of acute lymphoblastic leukemia with immunotherapeutic options

Clinical trial (acronym)	Participants	Condition	Intervention	Anticipated completion date
INO				
NCT03150693	310 adults	B-cell ALL, newly diagnosed	INO+ Chemotherapy vs. Chemotherapy	August 2024
BLIN				
NCT03476239	120 adults	B-cell ALL, Relapsed/ Refractory	BLIN	November 2021
NCT02101853	598 children, adults	B- cell ALL, first relapse	BLIN vs. Chemotherapy	Not available
NCT02393859	202 children	B-cell ALL, first relapse	BLIN vs Conventional Consolidation Chemotherapy	July 2023
NCT02003222	509 adults	B-cell ALL, newly diagnosed	BLIN + Chemotherapy vs. Chemotherapy	Not available
NCT03643276	5000 children	B-cell ALL, newly diagnosed with high risk of relapse	BLIN + Chemotherapy vs. Bortezomib + Chemotherapy vs. Chemotherapy	July 2028
TISA				
NCT03391739 (CCFRRBA)	20 children, adults	B-cell ALL, Relapsed/ Refractory	TISA	December 2019
NCT03027739 (CCFMPCA)	20 children, adults	ALL, refractory or high risk of relapse with positive minimal residual disease	TISA	December 2020
INO, BLIN, and TISA				
NCT03628053 (OBERON)*	220 adults	ALL, relapsed/ refractory	TISA ± Chemotherapy vs BLIN or INO ± Chemotherapy	December 2022

ALL- Acute lymphoblastic leukemia; BLIN- Blinatumomab; INO- Inotuzumab ozogamicin; TISA- Tisagenlecleucel

* Not yet recruiting