The Use of Blinatumomab Post Allogeneic Hematopoietic Cell Transplantation to Reduce the Risk for Disease Recurrence for Patients with B-lineage Acute Lymphoblastic Leukemia

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1.0 Objectives

1.1 Primary: To assess the feasibility of blinatumomab post allogeneic hematopoietic cell transplantation (HCT) as consolidation therapy in patients with B-lineage acute lymphoblastic leukemia (ALL). Toxicities attributable to blinatumomab, acute GVHD, and secondary graft failure will be the parameters to define feasibility.

1.2 Secondary:
1.2.1 To evaluate the progression-free survival (PFS) rate at 1-year for patients with ALL compared to contemporary patient cohort.

1.2.2 To evaluate other efficacy endpoints such as overall survival (OS) and minimal residual disease (MRD) negativity rate in patients treated with blinatumomab for consolidation therapy.

1.2.3 To evaluate, non-relapse mortality (NRM) and chronic GVHD.

2.0 Background

2.1 Risk for relapse following HCT

Allogeneic HCT is a curative approach for a select group of patients with ALL. Overall survival (OS) ranges from 30%-60% depending on the patients disease stage and risk profile at time of transplant (1,2). Increasingly, minimal residual disease (MRD), both before and after HCT, is becoming an important predictor for relapse (3). In a series of 149 ALL patients transplanted in remission at MD Anderson Cancer Center, patients with MRD, measured by multiparameter flow cytometric immunophenotyping (FCI) with a sensitivity of 0.01%, present at time of HCT had a shorter PFS compared to patients who were MRD negative, 28% vs. 47%, p=.08 (4). Furthermore, among 135 patients who had MRD measured following HCT, 20 became positive for MRD, and 18 of these patients developed

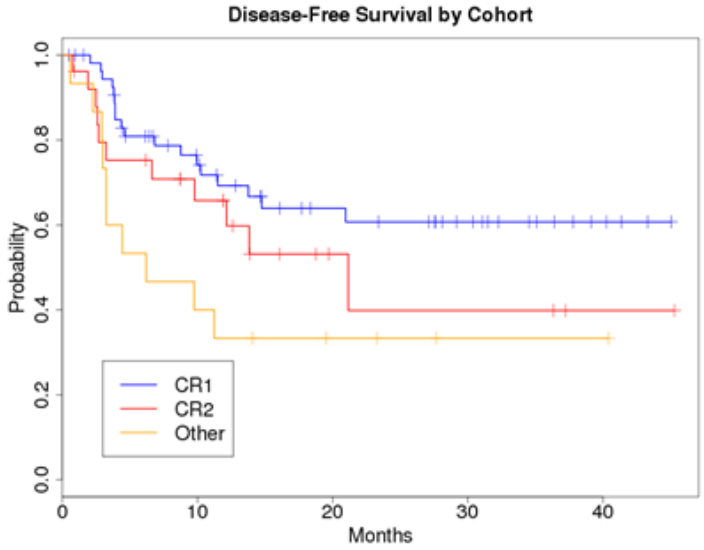
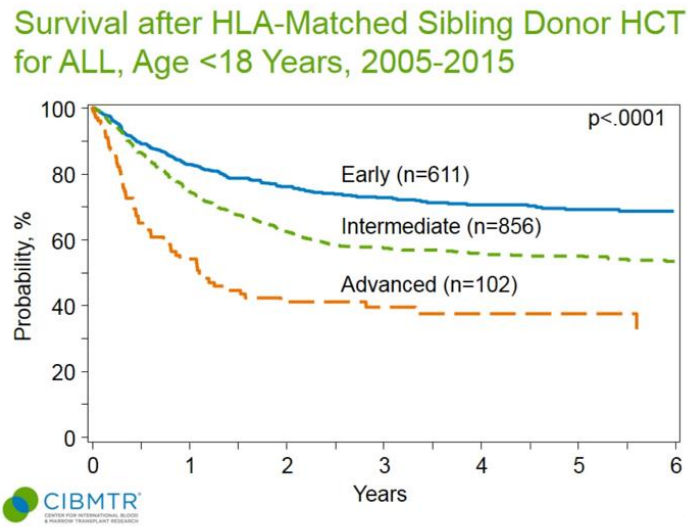


Figure 1. With a median follow-up of 13 months, 2-year DFS rates are 61%, 40% and 33% for patients in CR1, CR2, and more advanced disease respectively.

overt hematologic relapse within a median of 3.8 months (4). Of note, among 32 patients with overt relapse following HCT, 41% did NOT have preceding MRD, suggesting that positive MRD post HCT essentially confirms eventual relapse, but negative MRD post HCT in a high-risk patient does not preclude relapse. Our findings corroborate similar published studies (5,6). Patients transplanted beyond second remission routinely have a significantly lower PFS and OS rates. In our study of 97 patients (CR1 51, CR2 29, others 17) treated with busulfan and clofarabine chemotherapy conditioning following a matched sibling (MSD) or matched unrelated donor (MUD) transplant, patients in CR1 had a significantly better disease free survival (DFS) compared with others (Figure 1). For patients in CR1, the 2-yr DFS rate was 61% with 9/51 patients relapsing at median 9 months, the 2-yr DFS rate was 40% for CR2, with 10/29 relapsing at median 3 months, and for patients with more advanced disease, the 2-yr DFS rate was 33% with 3/17 progressing at a median of 3 months. Our preliminary results with this regimen were similar (7). Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) corroborate our findings. Between 1996 and 2001, in patients less than 20 years-old, OS ranges from 25% for patients transplanted beyond first remission to 50% for sibling transplants in first remission. Similarly, in adult patients, greater than 20 years-old, the best outcome is noted in sibling transplants done in first remission with OS of 60%, as compared to 35% if transplants are performed beyond CR1 (CIBMTR Registry).

In pediatric patients with B cell precursor acute lymphoblastic leukemia, cure rates with chemotherapy (in combination with radiotherapy in certain situations) can be as high as 80-85%. Children with second or greater relapse or refractory disease have dismal prognosis even when treated with allogeneic stem cell transplantation which is usually reserved for patients with high-risk features (i.e. poor-risk cytogenetic markers), those who fail to achieve remission or relapse after standard or intensive chemotherapy. From the CIBMTR data base, among the 1,569 patients younger than 18 years receiving an HLA-matched sibling transplant for ALL between 2005 and 2015, the 3-year probabilities of survival were 73% ± 2%, 58% ± 2%, and 40% ± 5% for patients with early (CR1), intermediate (second or subsequent CR), and advanced disease (primary induction failure and advanced disease), respectively. The corresponding probabilities of survival among the 2,845 recipients of an unrelated donor transplant were 68% ± 2%, 56% ± 1%, and



43% ± 4%. Disease relapse represent the most common cause of death post-transplant.

No effective treatment options exist for patients who relapse following HCT. Multiple published series report less than 10% survival for these patients, regardless of the treatment modality used, with a median survival of 2-3 months (2,8). To date, the most common strategy employed to reduce relapse rates after HCT has usually involved some form of immune manipulation, ranging from donor lymphocyte infusion (DLI) to second transplant (9-12). However, although it has been consistently shown that patients with B-ALL who develop graft-versus-host-disease (GVHD) have less risk for relapse (13), DLI has not shown appreciable efficacy in this patient population; remission rates have been less than 10%, and have been associated with a high incidence of GVHD (14). Of note, the best responses to DLI in ALL occur when the DLI is administered prophylactically to prevent relapse (10); this approach has been demonstrated in pediatric patients but no data for prophylactic DLI has been reported in adults.

Thus, there is an unmet need for effective therapy for ALL patients at high risk for relapse following allogeneic HCT, with high risk defined as positive MRD and/or disease beyond first complete remission. Blinatumomab has demonstrated efficacy in both the MRD setting (15, 16) and for patients with active disease (17). Importantly, since its mechanism of action is through immune modulation rather than cytotoxicity, it has a favorable risk profile with minimal cytopenias noted in patients (18). Furthermore, a recent series of 9 pediatric patients (19) and our personal experience in patients treated with blinatumomab after relapse following HCT indicate a low risk for GVHD.

2.2 Blinatumomab

The Bispecific T-cell Engaging (BiTE) antibody blinatumomab represents the first agent in a class that redirects host T-cells to cell surface antigen-expressing cancer cells. Blinatumomab contains the variable domains of a CD19 antibody and a CD3 antibody which are joined by a non-immunogenic linker (20). Upon binding to CD19, the cytotoxic T cells become activated and induce cell death via the pore-forming perforin system. The drug was initially administered as an intermittent infusion two to three times weekly, but lack of activity and serious neurologic

toxicity caused the schedule of administration to be abandoned (20). Based on the short half-life of the drug and the mechanism of action, continuous infusion over several weeks were investigated. This drastically improved the activity of the drug, particularly in ALL, and helped reduce adverse effects.

2.3 Blinatumomab and MRD

The first study with blinatumomab used as continuous infusion evaluated its potential role in eradicating MRD (15). MRD-positivity in ALL almost universally heralds systemic relapse and confers poor prognosis. Patients treated in this study were in hematologic and morphologic CR, but had persistent or reappearing MRD during consolidation chemotherapy. Blinatumomab was given at a dose of 15 $\mu g/m^2$/day as a continuous infusion for 28 days every 6 weeks (14 days off) (15). After completing one cycle, responding patients could receive up to three additional consolidation cycles or proceed to ASCT if a donor is available. MRD conversion after one cycle was observed in 16 of 20 evaluable patients (80%). In a long-term follow up update (median observation time 33 months), 12 of the 20 patients remained in CR. The estimated 3-year relapse-free survival was 60% (16). Nine patients underwent ASCT, but interestingly, non-transplanted patients had similar favorable outcome compared to the transplant group. Most relapses after blinatumomab treatment occurred early, within seven months of the start of therapy. In a confirmatory open-label multicenter phase II trial in 116 patients in morphologic CR with positive MRD positive, the overall rate of conversion to the MRD negativity was 80% (78% occurring after one cycle of treatment) (21).

2.4 Blinatumomab in relapsed and refractory ALL

Blinatumomab was subsequently studied in patients with active systemic ALL relapse. In a confirmatory open-label, single-arm, multicenter phase II study in 189 patients with relapsed-refractory disease, blinatumomab was administered as the overall response rate was 43% with 80% of the responses occurring within cycle 1. The median response duration and overall survival were 9 and 6 months, respectively (Table 1) (17).

In a pediatric phase I/phase II study of blinatumomab in relapsed/refractory ALL (defined as second or later bone marrow relapse, any marrow relapse after ASCT, or refractory to other treatments, and had > 25% blasts in bone marrow), among the 70 patients (median age 8 years, range 7 months to 17 years) who received the recommended dosage (15 $\mu g/m^2$/day for 28 days and 2 weeks treatment free per cycle), 27 (39%) achieved CR within the first two cycles, 14 (52%) of whom achieved complete minimal residual disease response. 40 out of 70 (57.1%) had undergone allogeneic HSCT prior to receiving blinatumomab, and 39 out of 70 (55.7%) had refractory disease. The median number of treatment cycles was 1 (range 1 to 5) (23).

2.5 Blinatumomab toxicity profile

The toxicity profile of blinatumomab has been largely consistent with historical studies, with fever, chills, and hypogammaglobulinemia occurring frequently. Tremor, headache, and other mental status changes (e.g., confusion) have been reported. Fever, chills, and other constitutional symptoms are thought to be due to a cytokine release syndrome that occurs shortly after the start of therapy and are reduced with the use of steroids (e.g. dexamethasone 8-24 mg daily x 2-3 days). The adverse effects coincided with a rapid rise in activated T-cells after blinatumomab initiation, essentially confirming the hypothesis (22). Life-threatening neurologic adverse events were uncommon and generally reversible, but seizures have been observed in both the MRD and the active disease studies. Corticosteroids before the first dose and prior to dose escalation ameliorate some of the toxicities.

The adverse reactions in pediatric patients treated with blinatumomab were similar to those seen in adult patients with relapsed or refractory B-cell precursor ALL. Adverse reactions that were observed more frequently in the pediatric population compared to the adult population were pyrexia (80% vs. 61%), hypertension (26% vs. 8%), anemia (41% vs. 24%), infusion-related reaction (49% vs. 34%), thrombocytopenia (34% vs. 21%), leukopenia (24% vs. 11%), and weight gain (17% vs. 6%). In infants and children < 2 years of age, the incidence of neurologic toxicities was not significantly different than for the other age groups, but its manifestations were different (agitation, headache, insomnia, somnolence, and irritability). In the phase I/II open label blinatumomab study in pediatric patients with relapsed / refractory ALL, among the 70 pediatric patients treated on the trial, the most frequent grade 3 adverse events were anemia (36%), thrombocytopenia (21%), and hypokalemia (17%). Three patients (4%) and one patient (1%) had cytokine-release syndrome of grade 3 and 4, respectively. Two patients (3%) interrupted treatment after grade 2 seizures. Reports of compassionate use of blinatumomab in pediatric patients with relapsed / refractory ALL and prior ASCT have shown that blinatumomab did not induce nor exacerbate acute graft versus host disease (24, 25).

3.0 Drug Information

3.1 Blinatumomab

Each BLINCYTO (blinatumomab) package contains 1 vial BLINCYTO and 1 vial IV Solution Stabilizer.

BLINCYTO is supplied in a single-use vial as a sterile, preservative-free, white to off-white lyophilized powder for intravenous administration. Each single-use vial of BLINCYTO contains 35 mcg blinatumomab, citric acid monohydrate (3.35 mg), lysine hydrochloride (23.23 mg), polysorbate 80 (0.64 mg), trehalose dihydrate (95.5 mg), and sodium hydroxide to adjust pH to 7.0. After reconstitution with 3

mL of preservative-free Sterile Water for Injection, USP, the resulting concentration is 12.5 mcg/mL blinatumomab.

IV Solution Stabilizer is supplied in a single-use vial as a sterile, preservative-free, colorless to slightly yellow, clear solution. Each single-use vial of IV Solution Stabilizer contains citric acid monohydrate (52.5 mg), lysine hydrochloride (2283.8 mg), polysorbate 80 (10 mg), sodium hydroxide to adjust pH to 7.0, and water for injection.

Since blinatumomab will be administered via continuous intravenous route, it needs to be stabilized at low concentrations to prevent absorption to surfaces. Therefore, the IV bag must be conditioned by prior addition of a product-specific diluent (IV solution stabilizer), resulting in a final diluent concentration of 0.5 mM citrate, 25 mM lysine hydrochloride and 0.002% (w/v) polysorbate 80. Sterile water for injection and supplies required for reconstitution and injection of blinatumomab will not be provided to clinical sites.

Risk of Serious Adverse Reactions in Pediatric Patients due to Benzyl Alcohol Preservative:
Gasping syndrome (central nervous system depression, metabolic acidosis and irregular respiration) is a serious and potentially fatal adverse reaction in infants treated with benzyl alcohol-preserved drugs. The 7 days bag of BLINCYTO solution for infusion with benzyl alcohol is not recommended for use in pediatric patients weighing < 22 kg. Consider the combined daily load of benzyl alcohol from all sources (including BLINCYTO) when prescribing BLINCYTO to pediatric patients.

3.1.2 Blinatumomab dosage, administration, and schedule

Blinatumomab is administered as a continuous intravenous infusion (CIV).
A single cycle of blinatumomab treatment is 4 weeks of CIV. Since patients are either in remission, or have minimal residual disease at time of treatment, the dosing schedule for minimal residual disease will be followed. Additionally, since both children and adults will be treated on this study, dosing will be weight- and BSA-based as per FDA guidelines for this drug. Please see section 5.3 for details of dosing administration.

The drug administration should not be interrupted, if possible. In case of infusion interruption, due to any technical or logistic reason, the interruption should be as short as possible and the infusion continued at the earliest time possible. Every interruption longer than 1 hour should be documented. If the interruption is longer than 4 hours, re-start of the infusion should be performed under healthcare supervision. The patient should be observed overnight for possible side effects after the restart in the hospital. Administration of dexamethasone premedication as described in Table 3 is recommended. If possible, the infusion duration before and after an interruption should total 28 days per treatment cycle.

3.1.3 Blinatumomab inpatient dosing

It is recommended that subjects are hospitalized at least during the first 3 days of the first induction cycle and the first 2 days of the following cycles.

The infusion bags will be changed by site nursing personnel trained on the protocol and on the proper administration of blinatumomab. Close monitoring during the first 48 hours of treatment in the first 2 cycles will be indicated because of the potential adverse events associated with T-cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab.

3.1.4 Blinatumomab outpatient dosing

After a patient meets the minimum criteria for inpatient administration and monitoring as described in the above section, and if a subject is deemed stable by the Principal Investigator or designee, continuation of blinatumomab infusion may continue as an outpatient.

In the outpatient setting, either the subject will return to the study site for changes of infusion bags or the subject will be visited by a well-trained ambulant/home care service provider at specific intervals to change the infusion bag. The subject and the ambulant/home care provider will be trained and will receive written instructions for storage of the IV bags.

In the event of drug interruptions of >4 hours, the restart of the infusion should be performed in the clinic/hospital under the supervision of their healthcare provider.

In case of any adverse event in the outpatient setting, the ambulant/home care provider should directly contact their healthcare provider at the study center for further management.

3.2 Dexamethasone premedication

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment. Within 1 hour before the start of treatment in each treatment cycle, mandatory premedication with dexamethasone at 20 mg IV if ≥ 45 Kg (or 5 mg/m^2 to a maximum of 20 mg if < 45 Kg) IV is required for the prevention of CRS resulting from blinatumomab (Table 1).

3.3. Dose modifications (interruptions, withholdings, and criteria for restarting treatment) (Tables 1 and 2).

3.3.1 Infusion interruption/dose modification due to adverse events
Common Terminology Criteria for Adverse Events (CTCAE) grade 4 adverse events at least possibly related to blinatumomab will require permanent

discontinuation of blinatumomab. For CTCAE grade 4 adverse events that are numerically defined laboratory parameters, independent investigator assessment should be used to determine the risk: benefit for each individual patient to continue or discontinue blinatumomab treatment.

For CTCAE grade 3, cytokine release syndrome, and CTCAE grade 3 DIC/coagulopathy, treatment with blinatumomab will be interrupted until the event resolves to at least grade 1. Blinatumomab can then be restarted at the lowest starting dose (9 µg/day if ≥ 45 Kg or 5 µg/m^2/day if < 45 Kg). If the AE lasts for ≥ 2 weeks, then blinatumomab will be permanently discontinued.

For all other CTCAE grade 3 events and clinically significant laboratory value changes, investigator assessment should be used to determine the risk: benefit to continue blinatumomab therapy with or without dose reduction or discontinue therapy.

Patients who have been dose reduced will have an option to receive the higher dose level once the AE has resolved to grade 1 or less for at least 7 days. Re-start of the infusion should be performed in the hospital. Before blinatumomab is re-started, premedication with dexamethasone 20 mg if ≥ 45 Kg (or 5 mg/m^2 if < 45 Kg) IV is required. The patient should be observed overnight for possible side effects after the restart in the hospital.

In addition to the events described above, the dose may be temporarily or permanently reduced to 9 µg/day if ≥ 45 Kg (or 5 µg/m^2/day if < 45 Kg) if, by investigator´s judgment, it is necessary for safety reasons. After at least 7 days of dosing at 9 µg/day if ≥45 Kg (or 5 µg/m^2/day if < 45 Kg), the dose may be increased to 28 µg/day if ≥ 45 Kg (or 15 µg/m^2/day if < 45 Kg) or treatment may be continued at the dose of 9 µg/day after consultation with the investigator.

If the interruption after an adverse event is no longer than 7 days, the same cycle will be continued. The infusion duration, before and after an interruption, should total 28 days per treatment cycle. If an interruption due to an adverse event is longer than 7 days, a new cycle will start. In addition, an incomplete treatment cycle with a treatment duration of less than 2 weeks will have to be repeated (eg, if cycle 1 was interrupted on day 8 for more than 7 days, the next cycle will be denoted as cycle 1.1 and the same assessments will be performed as in cycle 1). For cycle 1.1, subjects will be started at 9 µg/day if ≥ 45 Kg (or 5 µg/m^2/day if < 45 Kg) for the first 7 days of dosing followed by a dose step to 28 µg/day if ≥ 45 Kg (or 15 µg/m^2/day if < 45 Kg) beginning at day 8 and continuing for the remainder of cycle 1.

An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab will lead to permanent discontinuation of treatment. In case of logistical difficulties, restart of treatment can be postponed for up to 5 additional days without resulting in permanent treatment discontinuation.

Treatment may be also interrupted or permanently discontinued at the discretion of the investigator if any clinical/laboratory adverse event is considered to be medically relevant.

In case of signs of cytokine release, dexamethasone should be administered orally or IV at a dose of at maximum 3 x 8 mg/day for subjects ≥ 45 Kg (or 0.2-0.4 mg/kg/day divided 3-4 times per day not to exceed 24 mg/day for subjects < 45 Kg) for up to 3 days. The dose can then be reduced step-wise over 4 days.

3.3.2 Infusion interruption/dose modification due to CNS events
In case of CNS-related adverse events, dexamethasone should be administered at a dose of at least 24 mg/day for subjects ≥ 45 Kg (or 0.2-0.4 mg/kg/day divided 3-4 times per day not to exceed 24 mg/day for subjects < 45 Kg). The dexamethasone dose will then be reduced step-wise over 4 days.

In case of CTCAE grade 3 or higher CNS-related adverse events, blinatumomab will be stopped immediately and a physical exam, vital signs and safety laboratory tests will be performed. Additional measures can be taken upon discretion of the investigator, depending on the nature of the adverse event. Diagnostic measures to exclude potential infectious causes should be conducted after CNS events ≥ CTCAE grade 3; an assessment of cerebrospinal fluid should be performed for cytology, cell count, B- and T-cell measurement (flow cytometry at local lab), and viral studies (HSV 1/2, HSV6, JC virus and adenovirus), and magnetic resonance imaging (MRI).

Patients, who had experienced a Grade 3 CNS AE or SAE leading to treatment interruption, should have a treatment free interval of two weeks, even if the event has resolved to Grade 1 earlier. These patients will have to undergo MRI before treatment is resumed. Infusion should be re-started in the hospital, under supervision of the investigator and the patient should remain hospitalized for at least two days.

Following dexamethasone premedication, a new treatment cycle will start with a dose of 9 µg/day if ≥ 45 Kg (or 5 µg/m^2/day if < 45 Kg). Blinatumomab will be escalated to 28 mcg/day if ≥ 45 Kg (or 15 µg/m^2/day if < 45 Kg) after 7 days if the toxicity does not recur. If the toxicity occurs at 9 mcg/day if ≥ 45 Kg (or 5 µg/m^2/day if < 45 Kg)., or if the toxicity takes more than 7 days to resolve, blinatumomab therapy will be stopped permanently.

If the CNS event was a seizure (CTCAE grade 2 or above), appropriate prophylactic anticonvulsant treatment will be administered during the next treatment cycle.

A grade 3 CNS event leading to treatment interruption at the dose of 9 µg/day if ≥ 45 Kg (or 5 µg/m^2/day if < 45 Kg) or a CNS event needing more than 1 week to resolve to grade ≤ 1 will result in permanent treatment discontinuation.

In case of CNS-related events CTCAE Grade 4 or in case of occurrence of more than one seizure the infusion of blinatumomab will have to be stopped immediately and treatment will be permanently discontinued. For patients who discontinue treatment because of a CNS event ≥ Grade 3 an MRI is recommended. For patients in the additional evaluation cohort, an MRI is required after CNS event grade 3 or higher, regardless of continuation of treatment with blinatumomab.

Table 1. Dexamethasone premedication

Treatment phase	**Target patient**	**Dexamethasone dose**	
		Patient Weight	
		≥ 45 Kg	**< 45 Kg**
Pre-dose dexamethasone before each blinatumomab treatment	All patients (before each cycle and dose increase)	20 mg IV within 1 hour before start of treatment in each treatment cycle, and within 1 hour before dose increase	5 mg/m^2 IV within 1 hour before start of treatment in each treatment cycle, and within 1 hour before dose increase
Infusion interruption/dose modification due to adverse event	Patients who interrupt treatment > 4 hours	Dexamethasone 20 mg IV within 1 hour before re-start of treatment	5 mg/m^2 IV within 1 hour before re-start of treatment
In case of signs of cytokine release (CRS)	Patients with signs of CRS	Dexamethasone orally or IV at a dose maximum 3 x 8 mg/day for up to 3 days. The dose should then be reduced step-wise over 4 days	Dexamethasone orally or IV at a dose 0.2-0.4 mg/kg/day divided 3-4 times per day not to exceed 24 mg/day for up to 3 days. The dose should then be reduced step-wise over 4 days
Infusion interruption/dose modification due to CNS events	Patients with CNS-related AE	Dexamethasone should be administered at a dose of at least 24 mg/day. Dexamethasone will then be reduced step-wise over 4 days.	Dexamethasone should be administered at a dose of 0.2-0.4 mg/kg/day divided 3-4 times per day not to exceed 24 mg/day. Dexamethasone will then be reduced step-wise over 4 days.

Table 2. Management of Toxicity and Blinatumomab Dosage Adjustments

Toxicity	Grade	Action	
		Patient Weight	
		≥ 45 Kg	< 45 Kg
Cytokine Release Syndrome (CRS)	Grade 3	Withhold blinatumomab until resolved, then restart blinatumomab at 9 mcg/day Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	Withhold blinatumomab until resolved, then restart blinatumomab at 5 $\mu g/m^2$/day. Escalate to 15 $\mu g/m^2$/day after 7 days if the toxicity does not recur.
	Grade 4	Discontinue blinatumomab permanently	
Neurological Toxicity	Seizure	Discontinue blinatumomab permanently if more than one seizure occurs	
	Grade 3	Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than Grade 1 (mild) and for at least 3 days, then restart blinatumomab at 5 $\mu g/m^2$/day. Escalate to 15 $\mu g/m^2$/day after 7 days if the toxicity does not recur. If the toxicity occurred at 5 $\mu g/m^2$/day, or if the toxicity takes more than 7 days to resolve, discontinue blinatumomab permanently.
	Grade 4	Discontinue blinatumomab permanently	
Other Clinically Relevant Adverse Reactions	Grade 3	Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently.	Withhold blinatumomab until no more than Grade 1 (mild), then restart blinatumomab at 5 $\mu g/m^2$/day. Escalate to 15 $\mu g/m^2$/day after 7 days if the toxicity does not recur. If the toxicity takes more than 14 days to resolve, discontinue blinatumomab permanently
	Grade 4	Discontinue blinatumomab permanently	

4.0 Patient Eligibility

4.1 Inclusion Criteria:

1. Patients 1-70 years of age.

2. Patients with B-lineage ALL in a) hematologic complete remission (CR) beyond CR1 at time of transplant; b) primary induction failure defined as requiring more than one line of induction therapy; c) positive minimal residual disease defined by positive flow >0.01% before or after transplant; or d) high risk cytogenetic or molecular features consisting of Ph-like phenotype, detection of BCR-ABL transcript by PCR with a sensitivity of 1/10,000, or detection of the t(9;22) translocation in any metaphases by cytogenetics at time of transplant, or presence of the MLL gene before or after transplant.

3. Received an allogeneic HCT within the last 100 days. Enrollment within 30-100 days after transplant, and after adequate recovery of counts defined as ANC >/= 0.5 x 10^9/L without daily use of myeloid growth factor and platelet > 20 x 10^9/L without platelet transfusion within 1 week, and adequate organ function to receive blinatumomab defined as creatinine clearance greater than 30 ml/min (or greater than 60 ml/min/1.73), ALT/AST < 5 x ULN and serum bilirubin < 3 x ULN.

4. Performance status of 0, 1, or 2. Karnofsky (or Lansky for subjects < 16 years old) performance status ≥ 50.

4.2 Exclusion criteria:

1. Relapsed ALL defined as >5% malignant blasts in bone marrow or peripheral blood.

2. Active GVHD requiring systemic steroid therapy. Medications for GVHD prophylaxis are acceptable.

3. Systemic steroid therapy unless for physiologic replacement

4. Uncontrolled disease/infection as judged by the treating physician

5. Active ALL in the central nervous system (CNS), as defined by ≥5 leukocytes per µL with identifiable blast cells in the CSF (CNS 3 disease), and/or the presence of cranial-nerve palsies.

6. Pregnant or nursing women

5.0 Treatment Plan

5.1 This is an open-label, single-arm, phase II clinical study.

5.2 All patients will be registered through Core. All of the enrolled subjects' concomitant medications will be collected and readily available in the MDACC electronic medical record and will not be entered into the CRF.

5.3 Patients will receive blinatumomab as continuous intravenous infusion over 4 weeks.

Since this study includes children and adults, dosing will be weight and BSA-based as per FDA approved dosing guidelines:

For patients >/= 45 kg, the dose is 28 mcg/day administered as a continuous infusion on days 1-28 of each cycle.

For patients < 45 kg the dose is 15 mcg/m^2/day (maximum 28 mcg/day) administered as a continuous infusion on days 1-28 of each cycle

All patients will receive 4 cycles of blinatumomab, with first cycle administered within the first 3 months following HCT, and then at 6 (+/- 2 weeks), 9 (+/- 2 weeks), and 12 (+/- 2 weeks) months following HCT (day of hematopoietic progenitor cell infusion). This schedule was selected to allow for treatment with blinatumomab during the one year following transplant when patients are at risk for relapse while the GVL effect is maturing and becoming robust.

5.4 GVHD prophylaxis will be as institutional standard.

5.5 CNS prophylaxis will be as institutional standard. However, craniospinal radiotherapy for prophylaxis post HCT is not permitted.

5.6 Tyrosine kinase inhibitor (TKI) use for patients with Ph+ ALL will be left to the investigator's discretion.

6.0 Study Evaluations

6.1 Pretreatment Evaluation

Table 3. Pre-treatment evaluation schedule

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by IRB	Within 14 days before therapy
Medical History	History of present illness, known allergies, prior cancer history as far as traceable including ALL regimens and drugs uses, and past medical/ surgical history as far as relevant.	Within 14 days of therapy
Physical Examination	Vital signs (temperature, heart rate, respiratory rate, blood pressure) and performance status.	Within 14 days of therapy
Concomitant Medications	Document concomitant medications, excluding prn and supportive care medications	Within 14 days of therapy
Hematology	CBC with differential and platelet count	Within 14 days of therapy
Biochemistry	at least creatinine, total bilirubin, uric acid, LDH, SGPT or SGOT, tacrolimus.	Within 14 days of therapy
Pregnancy test	Serum or urine, if female *and/*of child-bearing potential only	Within 14 days of therapy
Bone marrow	Aspirate and/or biopsy with flow cytometry for confirmation of diagnosis; cytogenetics	Within 30 days of therapy
Peripheral blood	Chimerism assessment	Within 30 days of therapy
Lumbar puncture	To assess for CNS disease, as clinically indicated	Within 30 days of therapy
Imaging studies	Chest X-ray and/or PET/CT as clinically indicated	Within 30 days of therapy

6.2 Evaluation during study

Table 4. Evaluation During Study

Procedure	Comments	Schedule
Hematology	CBC with differential and platelet count	Weekly during each cycle
Biochemistry	at least creatinine, total bilirubin, SGPT or SGOT, tacrolimus	Weekly during each cycle
Physical Examination	Focused physical examination, including assessment for GVHD	Prior to each treatment cycle, and at study completion
Bone marrow	Aspirate and/or biopsy, MRD by multicolor flow cytometry, cytogenetics	Prior to each treatment cycle, and at study completion will be per the PI or treating physician discretion
Peripheral blood	Multiparameter FCI for immune reconstitution and PB chimerism	Prior to each treatment cycle, and at study completion will be per the PI or treating physician discretion
Optional Procedure: Peripheral blood	For banking in Dr. Rezvani's laboratory at MDACC	Prior to each treatment cycle, at day 7 (+/-2 days), day 14 (+/- 2 days) and at completion of each treatment cycle.

6.3 Evaluation of Toxicity
Toxicities will be graded according to the NCI Expanded Common Toxicity Criteria, version 4.

7.0 Criteria for Removal from the Study

7.1 Completion of study at 1 year.

7.2 Non-compliance by the patient with protocol requirements.

7.3 Occurrence of CTCAE grade 4 adverse event probably or definitely related to blinatumomab.

7.4 An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab.

7.5 Occurrence of a CNS-related adverse event probably or definitely related to blinatumomab, and meeting one or more of the following criteria:

- More than 1 seizure
- A CNS-related CTCAE Grade 4 adverse event
- A CNS-related adverse event leading to treatment interruption that requires more than one week to resolve to CTCAE Grade ≤ 1
- A CTCAE Grade 3 CNS-related adverse event leading to treatment interruption that occurred at a dose of 9µg/day

8.0 Statistical Considerations

8.1 Patient Characteristics

Demographic and baseline characteristics will be summarized for all patients. Categorical measures will be summarized using frequencies and percentages, while continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum.

8.2 Primary Objectives

The primary objective in this trial is feasibility. Treatment-related toxicities attributable to blinatumomab, an excess rate of acute GVHD, and an excess rate of secondary graft failures will be the parameters to determine feasibility. The successful completion of the trial without reaching stopping rules will indicate that the primary objective of the trial was met. Cumulative incidence time to GVHD will be computed from the date of allogeneic HCT to the date of event. The cumulative incidence (CI) of GVHD will be determined using the competing risks method. The competing risks included will be relapse and death, and patients who do not experience GVHD or relapse and are still alive at the last follow-up date will be censored at that date.

8.3 Secondary Objectives

8.3.1 Progression-free and Overall Survival

Progression-free Survival (PFS) will be defined from date of allogeneic HCT to the date of disease progression or death. Patients who are still alive at last follow-up date without disease progression will be censored at that date. OS will be defined from date of allogeneic HCT to date of last known vital sign. Patients who are still alive at the last follow-up visit will be censored. A contemporary cohort of patients with ALL being transplanted in first complete remission will be identified prospectively. PFS and OS will be estimated using the Kaplan-Meier method and differences between the patients receiving blinatumomab and the contemporary cohort will be determined using the log-rank test. Patient outcomes in the contemporary cohort will be stratified by MRD status.

8.3.2 Minimal Residual Disease

Patients who are MRD negative at the end of the study will be summarized using frequency and percentage.

8.3.3 Non-relapse Mortality

Non-relapse mortality (NRM) will be computed from date of allogeneic HCT to last known vital sign. The CI of NRM will be determined using the competing risks

method. The competing risk included will be relapse and patients who are still alive at the last follow-up date will be censored.

8.3.4 Safety Measures

Safety will be assessed by vital signs, laboratory assessments, adverse events, and serious adverse events for all treated patients. Categorical measures will be summarized using frequencies and percentages while continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum.

8.3.5 Continuous Toxicity Monitoring

Continuous monitoring of toxicity will be assessed for all treated patients, beginning with the first cohort of five patients. Assuming a prior beta distribution of (0.6, 1.4), the study will terminate if the Pr ($\delta t > 0.30 \mid$ data) > 0.85, where δt is the toxicity rate attributable to the treatment. Toxicities are defined as any 1) grade 3-4 acute GVHD greater than 30%, 2) secondary graft failure >30%, or 3) NRM within one cycle of blinatumomab (i.e., 30 days). The decision rule for terminating for toxicity is presented in Table 5 and the operating characteristics for this rule are presented in Table 6. The method used to produce the decision rule and operating characteristics was designed by Thall, Simon, and Estey (1995).

8.3.6

Infection rate will be summarized by frequencies and percentages.

Table 5. Stopping Boundaries

Total number of patients	**Stop if this many patients have toxicity:**
1-4	Never stop with this many patients
5	3-5
6-7	4-7
8-10	5-10
11-13	6-13
14-16	7-16
17-18	8-18
19-21	9-21
22-24	10-24
25-27	11-27
28-29	12-29
30	Always stop with this many patients

Table 6. Operating Characteristics

True % of DLTs	Pr (stopping early)	Median Sample Size (interquartile)
0.10	0.01	30 (30, 30)
0.20	0.10	30 (30, 30)
0.30	0.36	30 (13, 30)
0.40	0.72	13 (5, 30)
0.50	0.94	5 (5, 13)

9.0 Reporting Requirements

9.1 Treatment periods
Active treatment period is defined from the first day of treatment administration through 30 days after last dose given. The intensity of adverse events (AE) will be assessed according to the Common Terminology Criteria v4.0 (CTCAE). Adverse events and protocol deviations will be reported accordingly to MDACC policy and procedures. Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

9.2 Adverse events (toxicities) known to be produced by the transplant chemotherapy regimen:
Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis
Hepatic: self-limited elevations of liver function enzymes; veno-occlusive disease
Pulmonary: acute dyspnea, pulmonary fibrosis and interstitial pneumonitis.
Skin: rash.

9.3 Adverse events (toxicities) known to be produced by other treatment components:
The following events are not considered to be significant in relationship with the study treatment, would not be considered adverse events, and will not be collected in the study database.
Myelosuppression-related: neutropenia, anemia thrombocytopenia, platelets and RBCs transfusions.
Flu-like symptoms: low grade fever, headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia.
Mood alteration: depression, anxiety, and agitation
Readmissions (lasting <10 days)
Low blood pressure due to dehydration requiring fluid replacement
Fluid overload.

Fatigue.
Laboratory serum metabolic values not reflecting end-organ (hepatic, renal) function and or those considered associated to the original disease
Events that are identified to be related to the supportive treatment, e.g., steroids, palifermin, antibiotics.

9.4 Adverse Events Considered Serious (SAEs):

1. Graft failure/rejection
2. Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation)
3. Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
4. Any expected or unexpected event resulting in an irreversible condition and/ or leading to death.

SAEs will be reported to the PI or his designate, who in turn will notify the IRB following institutional policy.

9.5 Additional reporting requirements per study sponsor

The sponsor is responsible for compliance with expedited reporting requirements for serious and unexpected and related adverse events (SUSARs), for generation of SAE reports including narratives, and for periodic reporting to Amgen of SAEs

Safety Data	**Requirements**
Suspected Unexpected Serious Adverse Reaction (SUSARs)	Required (Sent to Amgen at time of regulatory submission)
Serious Adverse Events (SAEs)	Required (Cumulative listing to Amgen every 6 months)
Adverse Events not meeting serious criteria	Not required
Events of Interest	Not required
Pregnancy/Lactation	Required (Sent to Amgen within 10 days of Sponsor awareness)
Event listing for reconciliation	Required at end of study

*Specific requirements are to be outlined in the ISS Research Agreement

<u>Required Aggregate reports*:</u>

Safety Data	Timeframe for submission to Amgen
Annual Safety Report (eg, EU Clinical Trial Directive [CTD] Annual Safety Report, and US IND Annual Report)	**Annually**
Other Aggregate Analyses (any report containing safety data generated during the course of a study)	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc)
Final (End of Study Report), including: • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	**At time of ISS sponsor submission** to any body governing research conduct (eg, RA, IRB, etc) but not later than 1 calendar year of study completion

*Specific requirements are to be outlined in the ISS Research Agreement

10.0 References

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