Phase II Study of Blinatumomab in Patients with B-cell Lineage Acute Lymphocytic Leukemia with Positive Minimal Residual Disease

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1.0 Objectives

1.1 Primary Objectives: To evaluate the clinical efficacy of blinatumomab in patients B-cell acute lymphoblastic leukemia in complete morphologic remission with positive minimal residual disease (MRD) in terms of relapse-free survival RFS.

1.2 Secondary Objectives: To evaluate other efficacy endpoints such as overall survival and MRD negativity rate by flow cytometry and/or polymerase chain reaction (PCR) overall and after the first cycle, as well as safety of blinatumomab in this setting.

2.0 Patient Eligibility

Forty patients will be treated.

Inclusion Criteria:

1. Patients at least 18 years of age.

2. Patients with B-lineage ALL in hematologic complete remission (CR) with molecular failure (ie, had never achieved an MRD-negativity status before blinatumomab) or had a molecular relapse (ie, became MRD positive after having been MRD negative) starting at any time point after 3 months of frontline therapy. Molecular disease or minimal residual disease is defined by a value of at least of $1x10^{-4}$ (0.01%) by multicolor flow cytometry and/or by next generation sequencing (NGS)

3. Patients with B-lineage ALL in at least marrow CR in salvage 1 and beyond with molecular failure at any time point after 1 month of salvage therapy are allowed, including patients who received prior allogeneic stem cell transplantation.

4. Performance status of 0, 1, or 2

5. Adequate organ function with creatinine clearance ≥30 ml/minute and bilirubin less than or equal to 3.0 mg/dL.

6. No active or co-existing malignancy with life expectancy less than 12 months.

7. Patients with Ph+ ALL can be enrolled in CR1 or CR2 and beyond. A TKI will be added at the discretion of the treating physician. MRD for these patients will be defined by either 1.) a ratio of BCR-ABL1 to ABL1 by PCR of ≥ 0.01% according to the International Scale for patients with p210 transcript or a ratio of BCR-ABL1 to ABL1 by PCR of ≥ 0.01% for patients with non-p210 transcripts, or 2.) detectable MRD at a level of at least $1x10^{-4}$ (0.01%) by multicolor flow cytometry and/or by NGS.

Exclusion criteria:

1. Pregnant or nursing women

2. Known to be HIV+

3. Active and uncontrolled disease/infection as judged by the treating physician

4. Unable or unwilling to sign the consent form

5. Active CNS or extramedullary disease

6. Monoclonal antibodies therapy within 2 weeks before study entry

7. Radiotherapy and cancer chemotherapy (except for intrathecal prophylaxis and/or low-dose maintenance therapy such as vinca alkaloids, mercaptopurine, methotrexate, steroids) or any investigational drug within 2 weeks before study entry

3.0 Treatment Plan

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

3.2 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.

3.3 Patients will receive blinatumomab as continuous intravenous infusion at a dose of 28 µg/24 hours over 4 weeks followed by a treatment-free period of 2 weeks, defined as one 6-week treatment cycle. In the first induction cycle, the initial dose of blinatumomab will be 9 µg/day for the first 2 days of treatment (to mitigate for potential CRS and CNS events associated with introduction to blinatumomab) which then will be escalated (dose step) to 28 µg/day starting on day 3 through day 29 (week 4). For all subsequent cycles, 28 µg/day will be the dose for all 4 weeks of continuous treatment. Patients who weigh less than 45 kg at the start of each Blinatumomab cycle will have blinatumomab dosing discussed and approved by the principle investigator.

3.4 In patients, with an allogeneic donor, an allogeneic stem cell transplantation will be offered at any time after the first cycle of treatment with blinatumomab.

3.5 Responders will be permitted to receive up to four additional consolidation cycles of treatment with blinatumomab.

3.6 Patients who do not proceed with stem cell transplantation may receive blinatumomab maintenance therapy with one cycle every 3 months (±1 month) for up to 4 cycles.

3.7 CSF prophylaxis consisting of an intrathecal regimen according to institutional guidelines during and after blinatumomab treatment, will be left to the investigator's discretion.

3.8 Patients who remain in MRD remission for 3 months and then become MRD positive again can be retreated following the same treatment plan previously received.

4.0 Pretreatment Evaluation

Procedure	Comments	Schedule
Informed Consent	Obtain standard informed consent approved by IRB	Within 21 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
Neurologic exam	Full neurologic exam	Within 14 days of therapy
Concomitant Medications	Document concomitant 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	Within 14 days of therapy
Bone marrow	Aspirate and/or biopsy with flow cytometry/PCR for confirmation of diagnosis	Within 21 days of therapy
Lumbar puncture	To assess for CNS disease	Within 21 days of therapy
Pregnancy test	Serum or urine, if female of child-bearing potential only	Within 14 days of therapy
Imaging studies	Chest X-ray and/or PET/CT as clinically indicated	Within 14 days of therapy

5.0 Evaluation During Study

Procedure	Comments	Schedule
Hematology	CBC with differential and platelet count	Weekly during courses 1 to 5 and then during maintenance, within 1 week prior to each cycle of blinatumomab
Biochemistry	at least creatinine, total bilirubin, SGPT or SGOT	At least once every 2 weeks during course 1, then at least every 4 weeks during courses 2 – 5, and then during maintenance, within 1 week prior to each cycle of blinatumomab
Physical Examination	Focused physical examination	Prior to each blinatumomab course
Bone marrow	Aspirate and/or biopsy (MRD by flow multicolor cytometry and/or PCR and/or NGS).	On day 42 ± 7 days of the first course, then each cycle of blinatumomab until MRD negativity is achieved then every 2-3 cycles thereafter

5.1 Long-term Follow-up

Patients will be followed periodically every 6 months (+/- 3 months) for survival via brief phone call, even after being taken off

treatment. This may be done over the phone with a member of the study staff. The phone call should last about 10 minutes.

6.0 Criteria for Response

Primary criteria: MRD negativity
MRD levels will be continuously assessed during induction and consolidation therapy by 6-color multiparameter flow, PCR, and/or NGS.

For patients with Ph-negative ALL, MRD negativity is defined as undetectable MRD by flow cytometry with a sensitivity of at least 10^{-4}. For patients with Ph+ ALL, MRD negativity is defined as undetectable MRD by flow cytometry with a sensitivity of at least 10^{-4} AND absence of a quantifiable PCR for BCR-ABL1 by PCR with a sensitivity of at least 10^{-4} or a ratio of BCR-ABL1 to ABL1 by PCR of < 0.01% according to the International Scale for patients with p210 transcript or a ratio of BCR-ABL1 to ABL1 by PCR of < 0.01% for patients with non-p210 transcripts
No response (NR):
Patients will be considered non-responders if criteria for MRD negativity are not achieved after 2 cycles.

7.0 Background

7.1 Minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL). Persistence or reappearance of minimal residual disease (MRD) after induction chemotherapy is the most important adverse prognostic factor in patients with B-lineage acute lymphoblastic leukemia (ALL) and identifies chemorefractory disease.[1-6] More than 90% of patients who fail to clear MRD after chemotherapy experience a clinical relapse despite continued chemotherapy. The median time to relapse of patients with MRD+ disease is 4-5 months.[7] The only option to cure these patients is allogeneic hematopoietic stem cell transplantation (HSCT), but the outcome is suboptimal.[8]Therefore, the development of novel therapies with an alternative mode of action for the treatment of molecularly refractory B-lineage ALL is urgently needed.

7.2 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.[9] 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.[9] 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.

7.3 Blinatumomab and MRD

The first study with blinatumomab used as continuous infusion evaluated its potential role in eradicating MRD.[10] 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 mcg/m^2/day as a continuous infusion for 28 days every 6 weeks (14 days off).[11] 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%.[12] 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).The medians survival for responding patients was 39 months compared with 12 months in non-responding patients.[13]

7.4 Blinatumomab in relapsed and refractory ALL

Blinatumomab was subsequently studied in patients with active systemic ALL relapse. The results of this ongoing trial were updated recently (Table 1).[14] Three dose levels were explored, all involving blinatumomab administration as a continuous infusion for 28 days every 6 weeks. The overall response rate (CR or CR with incomplete count recovery) within two cycles of therapy was 69%. The estimated median survival was 9 months.[14] The final dose selected for future studies was 5 mcg/m^2/day during week one, and 15 mcg/m^2/day during the following three weeks and all subsequent cycles. In a confirmatory open-label, single-arm, multicenter phase II study in 189 patients with relapsed-refractory disease, 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).[15]
Following these results,61 a Phase III trial (TOWER study) was conducted in more than 400 patients with relapsed/refractory Ph-negative ALL randomized (2:1) to blinatumomab (n=271) or standard of care (n=134).[16] The response rates were 44% and 25%, respectively ($p<0.001$). Molecular remission rates among responders, defined as < 10-4 blasts in the first 12 weeks, were 76% and 48%, respectively. Blinatumomab prolonged survival, the primary study endpoint: the median OS was 7.7 months (5.6-9.6) versus 4.0 months (2.9-5.3; $p=0.01$; HR=0.71).

Table 1. Activity of blinatumomab in patients with relapsed/refractory ALL

	N (%)	
Parameter	Pivotal Study n=36	Confirmatory Study n=189
Response		
CR	15 (42)	62 (33)
CR with incomplete count recovery	10 (25)	19 (10)
All responders	25 (69)	81 (43)
Salvage Status		
Salvage 1	21 (58)	38 (20)
Salvage 2+	15 (42)	151 (80)
Median survival (months)	9.0	6.1

CR=complete response

7.5 Blinatumomab toxicity profile

Cytokine Release Syndrome (DRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO.

Serious adverse events that may be associated with CRS included pyrexia, headache,, nausea, asthenia, hypotension, increased alanine aminotransferase, increased aspartate aminotransferase, and increased total bilirubin; these events infrequently led to BLNCYTO discontinuation. Life-threatening or fatal CRS was infrequently reported in patients receiving BLNCYTO. In some cases, disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytoss/macrophage activation syndrome (HLH/MAS) have been reported in the setting of CRS.

In patients receiving BLINCYTO in clinical trials, neurological toxicities have occurred in approximately 50% of patients. The median time to onset of any neurological toxicity was 7 days. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 15% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and

disorientation, and coordination and balance disorders. The majority of events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation.

8.0 Background Drug Information

8.1 Blinatumomab

8.1.1 Investigational Product

In accordance with the protocol the following will be referred to as IP:

- Blinatumomab (AMG 103)

For each of the IP used, the preparation procedure(s) and storage condition(s) should comply with the instructions provided in this manual.

Description of Investigational Product

Blinatumomab (AMG 103)

Blinatumomab is a murine recombinant single-chain antibody construct combining both the binding specificity for the pan B-cell antigen CD19 and the epsilon chain of the T-cell receptor/CD3 complex on one polypeptide chain. It is monomeric, not glycosylated and weighs approximately 55 kilo Daltons (kDa). It belongs to a new class of bispecific antibody constructs called bispecific T-cell engagers (BITEÒ). Bispecific T-cell engagers have been designed to direct T-effector memory cells towards target cells. The proximity induced by the BITE® triggers target cell-specific cytotoxicity, which closely resembles standard cytotoxic T lymphocyte (CTL) activation. This T-cell–mediated target-specific killing is the therapeutic mechanism of action of blinatumomab.

Other Protocol-required Products.
The following protocol-required product(s) are not considered IP, but will be provided by Amgen:

IV Solution Stabilizer (IVSS)
The IVSS functions to prevent adsorption of blinatumomab to surfaces of the infusion components. The IVSS is not an Investigational Product per definition but will be referenced together with blinatumomab in this manual given that the storage conditions are identical. IVSS will be supplied with blinatumomab, but will be packed and labeled separately.

Infusion Pump:
Blinatumomab must be administered using programmable infusion pumps approved for use by the appropriate regulatory authority for the country in which the subject is undergoing treatment, in both the inpatient and outpatient settings. No elastomeric pumps are allowed. The infusion pump should be supplied by the trial site. If in individual cases the site cannot provide an appropriate pump,

alternative methods must be discussed with Amgen. Any provision via Amgen needs to be discussed with the Clinical Monitor.

For further information please refer to Section ”Devices”. This Section also includes requirements for IV bags, IV lines and inline filters.

8.1.2 Packaging and Formulation

AMG 103 (blinatumomab) and the IV Solution Stabilizer will be manufactured and packaged by Amgen Inc. or its agents, and distributed using Amgen or its agents’ clinical study drug distribution procedures.

Blinatumomab (AMG 103)
Blinatumomab is supplied in 4 mL single-use glass injection vials as a sterile, preservative-free, white to off-white lyophilized powder for reconstitution and administration by IV infusion. Each vial contains a target of 38.5 µg blinatumomab (nominal) formulated with 3.68 mg citric acid monohydrate, 105.0 mg trehalose dihydrate, 25.55 mg lysine hydrochloride, and 0.70 mg polysorbate 80, pH 7. Following reconstitution with 3 mL sterile water for injection (sWFI) the final concentration of blinatumomab will be 12.5 µg/mL. Blinatumomab is not considered cytotoxic.

IV Solution Stabilizer (IVSS)
The IV Solution Stabilizer is supplied in 10 mL single-use glass injection vials as a sterile, preservative-free, clear, colorless-to-slightly-yellow liquid concentrate. It consists of 25 mM citric acid monohydrate, 1.25 M L-lysine hydrochloride, and 0.1% (w/v) polysorbate80, pH 7.
Following dilution of the 50 x concentrate in 0.9% NaCl, the ingredient concentrations are 25 mM L-lysine hydrochloride, 0.002% (w/v) polysorbate 80, and 0.5 mM citric acid monohydrate.

Packaging of Blinatumomab / IV Solution Stabilizer:
US/Canada (North America), Mexico/Brazil (Latin America/South America), South Korea/Taiwan (Asia):
- Blinatumomab: 15 vials / box.
- IV Solution Stabilizer: 6 vials / box, both provided in separate boxes.

8.1.3 Blinatumomab dosage, administration, and schedule

Blinatumomab is administered as a continuous intravenous infusion (CIVI).
A single cycle of blinatumomab treatment is 6 weeks in duration, which includes 4 weeks of blinatumomab CIVI followed by a 2 week treatment-free interval. The treatment-free interval may be prolonged by up to 7 days, if deemed necessary by the investigator. In the first induction cycle, the initial dose of blinatumomab will be 9 µg/day for the first 2 days of treatment (to mitigate for potential CRS and CNS events associated with introduction to blinatumomab) which then will be

escalated (dose step) to 28 µg/day starting on day 3 through day 28 (week 4). For all subsequent cycles, 28 µg/day will be the dose for all 4 weeks of continuous treatment.

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 subject should be observed overnight for possible side effects after the re-start, either in the hospital or in the outpatient setting as applicable. 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. Patients who weigh less than 45 kg at the start of each Blinatumomab cycle will have blinatumomab dosing discussed and approved by the principle investigator.

8.1.4 Blinatumomab inpatient dosing

It is recommended that subjects are hospitalized at least during the first 4 days of the first induction cycle and the first 2 days of cycle 2. Hospitalization is at the discretion of the treating physician.
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.

8.1.4 Blinatumomab outpatient dosing
If a subject is deemed stable by the investigator, blinatumomab infusion may be initiated as an outpatient.

In the outpatient setting, the subject will return to the study site for changes of infusion 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 the investigator.

8.2 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 is required for the prevention of CRS resulting from blinatumomab.

8.3. Dose modifications (interruptions, withholdings, and criteria for restarting treatment) (Tables 2 and 3)

8.3.1 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.

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/d). 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 IV is required. The patient should be observed over night for possible side effects after the restart, either in the hospital or in the outpatient setting, as applicable.

In addition to the events described above, the dose may be temporarily or permanently reduced to 9 µg/day if, by investigator´s judgment, it is necessary for safety reasons. After at least 7 days of dosing at 9 µg/day, the dose may be increased to 28 µg/day 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 for the first 7 days of dosing followed by a dose step to 28 µg/day 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 7 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 8 mg every 8 hours for up to 3 days. The dose can then be reduced step-wise over 4 days.

8.3.2 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. 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).

Additional investigations of the CSF should be performed as clinically appropriate.

For subjects who experience a CTCAE grade 3 CNS adverse event or serious adverse event leading to treatment interruption, if the event has decreased to at least CTCAE grade 1 within 1 week, treatment may be restarted within 2 weeks, but not earlier than 72 hours (3 days) after the infusion was stopped.

After treatment interruption, a new treatment cycle may be started after consultation with the principal investigator. A contrast-enhanced magnetic resonance imaging (MRI) of the head will be performed for subjects who had to interrupt treatment because of a CNS event grade 3 before treatment is resumed. Infusion should be restarted in the hospital, and the subject should remain hospitalized for at least 2 days. Following dexamethasone premedication as described in Table 3, a new treatment cycle will start with a dose of 9 µg/day. Blinatumomab will be escalated to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurrs at 9 mcg/day, 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 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.

At the discretion of the investigator, an MRI should be considered for subjects who permanently discontinue treatment because of a CNS event ≥ grade 3.

Table 2. Dexamethasone premedication

Treatment phase	Target patient	Dexamethasone dose
Pre-dose dexamethasone before each blinatumomab treatment	All patients (before each cycle and dose increase)	Dexamethasone 20 mg 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
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
Infusion interruption/dose modification due to CNS events	Patients with CNS-related AE	Dexamethasone should be administered at a dose of at least 24mg/day. Dexamethasone will then be reduced step-wise over 4 days.

Table 3. Dosage Adjustments

If the interruption after an adverse event is no longer than 7 days, continue the same cycle to a total of 28 days of infusion inclusive of days before and after the interruption in that cycle. If an interruption due to an adverse event is longer than 7 days, start a new cycle.

Toxicity	Grade	Action

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
	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
	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
	Grade 4	Discontinue blinatumomab permanently

9.0 Evaluation of Toxicity

Toxicities will be graded according to the NCI Expanded Common Toxicity Criteria

10.0 Criteria for Removal from the Study

Criteria for removal from study include, but are not restricted to, the following:
10.1 No response after 2 cycles or progressive disease

10.2 Non-compliance by the patient with protocol requirements

10.3 Patient's request to be removed from the study

10.4 Occurrence of CTCAE grade 4 adverse event at least possibly related to 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.

10.5 Occurrence of an adverse event which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator's and/or the subject´s opinion

10.6 An infusion interruption of more than 2 weeks due to an adverse event related to blinatumomab (exception: in case of logistical difficulties, restart of treatment can be postponed for up to 7 additional days without resulting in permanent treatment discontinuation)

10.7 Occurrence of a CNS-related adverse event 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
- An MRI is recommended for subjects who discontinue treatment because of a CNS event ≥ Grade 3.

10.8 Investigator's decision that a subject does not benefit from treatment anymore, e.g., non-response or development of progressive disease

11.0 Statistical Considerations

This is a single-arm phase II study of blinatumomab in patients with B-cell ALL in morphologic remission with persistent MRD or MRD relapse. The primary objective is to evaluate the clinical efficacy of blinatumomab in this patient population. The primary efficacy endpoint is relapse-free survival, which is defined as the time interval from date of treatment start until the date of death or hematologic or extramedullary disease relapse. Patients who are alive and relapse-free at the last follow-up date will be censored at that time. In addition, patients who drop off the study due to receiving allogeneic stem cell transplantation will be censored at the time off study. Event-free survival is defined as RFS in addition to lack of achievement of negative MRD status after 2 cycles of blinatumomab (events will include death, lack of response after 2 cycles, and loss of response/progression, including MRD recurrence). Patients will be

followed for RFS, EFS, OS, and transplant-related morbidity and mortality after blinatumomab therapy. Patients in 2nd CR and beyond enrolled will reported separately.

The study will be continuously monitored for the primary endpoint, RFS, using the method of Thall, Wooten, and Tannir (2005). Our goal is to improve the median RFS from 7.2 months (based on historical treatment) by at least 6 months (deemed as clinically meaningful) using blinatumomab maintenance therapy. It is assumed that the RFS time is exponentially distributed with a median of λ_E among patients who receive blinatumomab as a maintenance therapy, and a median of λ_H is assumed for the historical treatment. Further, we assume that λ_H follows an inverse gamma distribution, i.e., $I_H \sim IG(7.184, 44.525)$, which has a mean of 7.2 months and variance of 10. To reflect the little prior knowledge of λ_E we assume an inverse gamma prior distribution with the same mean of 7.2 months and a much larger variance of 100, i.e., $\lambda_E \sim IG(2.518, 10.932)$. The trial will be stopped early if $Pr(\lambda_E > \lambda_H + \delta | data) < pL$, where $\delta = 6$ months and pL=0.03 and this futility monitoring rule will be first applied when 10 patients have been enrolled. A maximum of 40 patients will be enrolled into this study at an expected accrual rate of 1 patient per month. Patients will be followed up for an additional 18 months after all patients have been enrolled. The trial will be conducted using the Clinical Trial Conduct (CTC) website maintained by the Department of Biostatistics at MDACC.

The operating characteristics of the design, based on an overall assumed accrual rate of 1 patient per month with 1000 simulated trials per scenario, are given in the following table. OneArmTTE (version 2.2) was used for the design and simulation.

Scenario	True Median RFS (months)	Pr(Stopped Early due to futility)	Mean No. patients	Average Trial Duration (months)
1	6	0.984	15.7	33.7
2	7.2	0.869	20.7	38.7
3	10.2	0.305	33.0	51.0
4	13.2	0.087	37.8	55.8
5	16.2	0.032	39.2	57.0
6	19.2	0.020	39.4	57.5

In addition, we will continuously monitor treatment-related toxicities using the Bayesian approach of Thall, Simon, Estey (1995). Specifically, the trial will be stopped if $Prob(\pi T > 0.30 \mid data) > 0.90$, where πT is the toxicity rate and we assume a beta (0.6, 1.4) prior for πT. That is, if at any given time, there is more than 90% probability that the toxicity rate of the maintenance therapy with blinatumomab is greater than 30%, the trial will be stopped. For the purpose of toxicity monitoring, toxicities are defined as any treatment –related grade 3 or 4

non-hematologic AEs occurred any time during the trial. We will apply this stopping rule starting from the 5th patient and in cohort size of 5. The stopping boundaries corresponding to this toxicity monitoring rule are described in the following table:

Stopping boundaries for treatment-related grade 3, 4 non-hematologic toxicities

The number of patients evaluated for toxicities (in cohort size of 5)	Stop the trial if this many of patients with toxicities
5	4-5
10	6-10
15	8-15
20	9-20
25	11-25
30	13-30
35	15-35
40	Always stop with this many of patients

The operating characteristics for toxicity monitoring are described in the following table. MultcLean Desktop 2.1.0 was used for the design and simulations for toxicity monitoring.

Operating characteristics for Toxicity Monitoring

True Toxicity Rate	Early Stopping Probability	Sample Size		
		25th percentile	Median	75th percentile
0.10	0.0006	40	40	40
0.20	0.021	40	40	40
0.30	0.186	40	40	40
0.40	0.583	15	25	40
0.50	0.905	10	15	20

Analysis Plans

The probabilities of RFS and OS will be estimated using the method of Kaplan and Meier. For the primary analysis of the efficacy endpoint, we will compute the Bayesian posterior probability of $Pr(\lambda_E > \lambda_H + \delta|data)$, where δ = 6 months. As a secondary analysis, we will perform a competing risk analysis treating stem cell transplant as a competing event for RFS. In addition, we will assess the RFS and OS in the subgroup of patients with MRD positivity in at least marrow CR2 beyond; or in the subgroup of patients with and without ASCT, if permitted by the sample size. Landmark analysis may be performed to assess the difference in RFS or OS between patients with or without receiving ASCT, if permitted by the sample size. The MRD negativity rate will be estimated along with the exact 95% confidence interval. All treated patients are included in the safety analysis set.

The AEs will be summarized by organ type, grade and attribution to study treatment.

12.0 REPORTING REQUIREMENTS

12.1 Adverse Events Requiring Expedited Reporting: Serious unexpected adverse events (SAEs) considered associated with therapy should be reported as per institutional IRB policy and will be reported to Amgen upon submission to Regulatory Agency.

12.1.1 No individual SAE reports will be sent to Amgen, but SAEs will be reported as a cumulative line listing to Amgen every 6 months. The reporting timelines for logged SAEs and SUSARs will start with the patient's first dose and end 30 days following the last dose of study drug.

12.2 Expected Therapy Related Events

Only grade 3 and 4 related Adverse Events will be captured in a departmental database. Only the apogee will be recorded.

12.3 Events not considered to be serious events are hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition

12.3.1 Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.

12.3.2 Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

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