CITY OF HOPE
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DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A phase 1/2 trial of pembrolizumab in combination with blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia

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DISEASE SITE: Acute Lymphoblastic Leukemia (ALL)

STAGE: relapsed or refractory

MODALITY(IES): monoclonal antibody

TYPE: Phase I/2

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Clinical Trial Protocol

A phase 1/2 trial of pembrolizumab in combination with blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia

Version Date:	11/26/2024
Protocol Version:	10.1
City of Hope #:	19017
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IND Number:	139385
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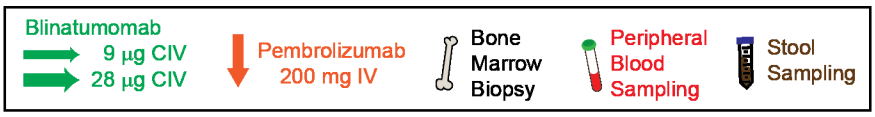
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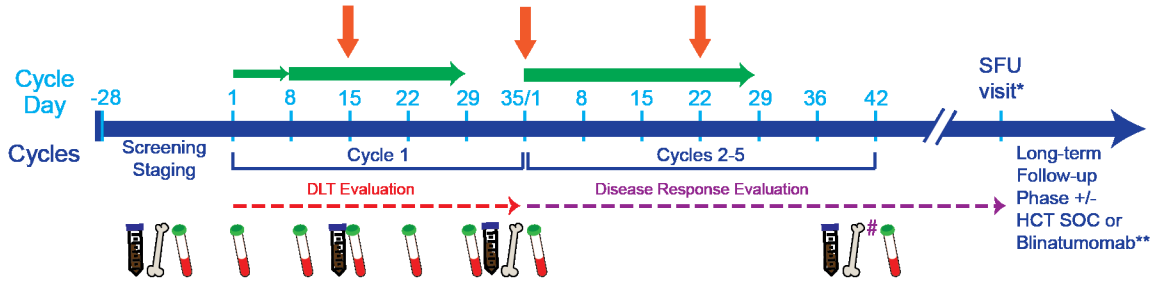
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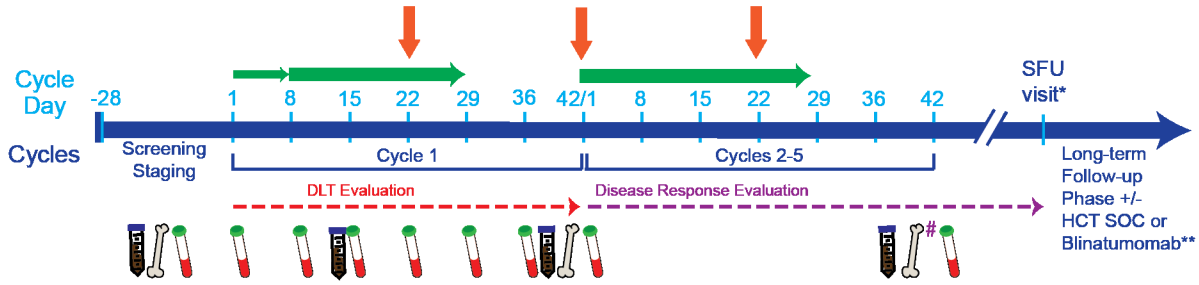
Treatment Schema



Schedule A



Schedule B



* Safety Follow-Up (SFU) visit: All subjects, including subjects who withdraw early, should complete a safety follow-up visit 30 days (± 3 days) after the last dose of study drug, or prior to further therapy/allogeneic hematopoietic stem cell transplant (alloHSCT), if applicable.

** Long-term Follow-Up (LTFU) Phase: Patients who have completed treatment will be followed for standard of care disease assessment (until disease progression) and survival for 1 year after start of therapy. Patients who complete treatment in complete response (CR) may opt to receive alloHSCT off protocol or to continue receiving blinatumomab as a single agent (per standard of care (SOC) schedule).

Bone marrow aspirates will be collected at the end of cycle 1 between 3 to 7 days before start of cycle 2 and 1 to 14 days before start of subsequent cycles at SOC marrow collection times until CR is documented (first of 2 consecutive leukemia-free biopsies). After CR is attained, biopsies for patients remaining on treatment will be within 2 weeks of the end of every other cycle until the end of treatment.

Note: Baseline stool samples will be collected at screening within 1 week of treatment start, prior to pembrolizumab administration and at the end of cycles 1 and 2.

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Protocol Synopsis

Protocol Title:
A phase 1/2 trial of pembrolizumab in combination with blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia
Brief Protocol Title for the Lay Public (if applicable):
Phase 1/2 Trial of Pembrolizumab and Blinatumomab in Acute Lymphoblastic Leukemia
Study Phase:
Phase 1/2
Participating Sites:
Single Center: City of Hope /Duarte, CA
Rationale for this Study:
Outcomes in patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) are dismal with median overall survival of four to six months in adult patients. In this setting, allogeneic hematopoietic stem cell transplantation (alloHSCT) has historically provided 40% long term remission if a second remission is achieved. However, second remission is often difficult to achieve with conventional chemotherapy. Recently blinatumomab (Blincyto®) has provided impressive efficacy in this patient population. Blinatumomab single-agent immunotherapy has led to a 41.6% complete response (CR)/CR with incomplete hematologic recovery (CRi) rate in patients with relapsed/refractory (R/R) ALL. Yet, there is still much to explore in the way of augmenting the therapeutic efficacy of blinatumomab. One potential avenue of augmenting the efficacy of blinatumomab is to exploit the PD-1/PD-L1 pathway in acute leukemia. The PD-1/PD-L1/L2 pathway has been shown to directly regulate the extent of cytolytic T cell function. Blocking PD-1/PD-L1/L2 pathway using anti-PD-1 antibodies has translated into overall survival benefit in patients with advanced melanoma, NSCLC and other solid and now hematologic malignancies. This pathway has also been shown to directly regulate the development, maintenance, and function of regulatory T cells (Tregs). The recent identification from Topps et al. that increasing the percentage or amount of Treg prior to blinatumomab therapy may predict response in R/R ALL patients is critical to this end. These investigators queried whether quantification of regulatory T cells can predict the outcome of blinatumomab therapy. In their analysis of 31 R/R ALL patients, those who were refractory to the treatment had higher numbers of Tregs as compared to responders. They subsequently sought to determine the mechanism by which Tregs may influence the immune response. Regulatory T cells incubated with blinatumomab and primary ALL blasts upregulated CD69, CD25 and PD-1. Here, we postulate that blocking PD-1/PD-L1 pathway using pembrolizumab will elicit anti-leukemic activity and that pembrolizumab can be safely administered together with blinatumomab thereby augmenting the therapeutic efficacy of blinatumomab in the treatment of patients with R/R ALL.

Objectives:

In adult patients with relapsed/refractory ALL:

Phase 1

Primary:

- Assess the safety and tolerability of combination immunotherapy with blinatumomab and pembrolizumab by evaluation of toxicities including: type, frequency, severity, attribution, time course and duration (secondary objective for phase 2 portion).
- Determine the recommended phase 2 schedule (RP2S) of combination immunotherapy with pembrolizumab and blinatumomab.

Phase 2 (Patients on RP2S of Phase 1 included)

Primary: Estimate the anti-leukemia activity of combination immunotherapy blinatumomab and pembrolizumab as assessed by overall response rate (CR or CRi).

Secondary (all evaluable patients):

- Assess the safety (phase 2 enrollment only);
- Estimate time to response (CR or CRi) and response duration;
- Estimate overall survival and event-free survival;
- Among transplant eligible patients, determine the number and proportion of patients who bridge directly from trial therapy to alloHSCT after completing at least the first cycle of combination therapy;
- Determine the number and proportion of patients who receive single-agent blinatumomab and the proportion able to complete the full 9 cycles of blinatumomab;
- Estimate the minimal residual disease (MRD) rate;

Study Design:

This study will be conducted as a single center, open-label, phase 1/2 clinical trial.

The study is designed to evaluate the safety and tolerability of pembrolizumab when combined with blinatumomab as part of a 6-week treatment cycle. The anti-leukemia activity of the combination therapy, among patients treated at the recommended phase 2 schedule, will also be assessed. In both Schedules A and B, the pembrolizumab (200mg) and blinatumomab doses (28 µg/day) are fixed, except that blinatumomab is given at 9 µg/day on days 1 to 7 during cycle 1.

Phase 1:

The phase 1 portion of the trial will implement traditional '3+3 rules' for enrollment with schedule 'reduction' (from Schedule A to Schedule B), or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs) during cycle 1.

Schedule[+]	Cycle Length	Pembrolizumab: 200mg	Blinatumomab: 28 µg/day† CIV
A (starting schedule)	35 days cycle 1, 42 days cycles 2–5	cycle 1[#]: day 15 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28
B*	42 days all cycles	cycle 1: day 22 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28

[+]: Enrolled patients may receive up to 5 cycles of treatment.
*: While it is believed that Schedule A will be well tolerated, one schedule 'reduction' is allowed, from Schedule A to Schedule B, in the presence of dose limiting toxicity. Under Schedule B, during cycle 1, initiation of pembrolizumab is delayed by 7 days and the treatment free interval is extended to 14 days.
#: The length of cycle 1 in Schedule A is 35 days. All other cycles in Schedules A and B are 42 days.
†: In cycle 1, on days 1-7 blinatumomab will be given at 9 µg/day

Depending on schedule assignment, the first cycle will be either 35 days (Schedule A) or 42 days (Schedule B). After Cycle 1, on both schedules patients will be treated in planned 42-day treatment cycles until disease relapse, progression, unacceptable toxicity, or other criteria for removal from study treatment are satisfied. Patients will undergo response evaluation using the NCCN ALL response criteria.

The schedule that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated schedule. The recommended phase 2 schedule of pembrolizumab/blinatumomab will generally be the maximum tolerated schedule, but it may be less than the maximum tolerated schedule based on a review of available data/cumulative toxicities. Once the maximum tolerated schedule/ recommended phase 2 schedule has been determined the phase 2 study of the combination will be initiated.

Phase 2:

The phase 2 portion will implement a Simon two-stage optimal design (Simon 1989; Jung 2004) to evaluate the anti-leukemia activity of the two-agent combination as assessed by overall response (CR, CRi) rate in patients with relapsed/refractory ALL. The study is expected to enroll and treat a minimum of 12 and a maximum of 30 patients at the recommended phase 2 schedule. The sample size is based on the desire to discriminate a promising CR/ CRi rate of 64% from a disappointing response rate of 44% using a type I error rate of 0.10 and power of 80%. At stage 1, 12 patients will be entered on the study. Note: The six patients treated at the recommended phase 2 schedule in the phase 1 portion of the study will count toward the 30 patients required; given this, we expect to enroll only 24 new patients on the phase 2 trial. If ≤ 5 complete remissions are seen, the study will be terminated. If at least 6 patients achieve CR/ CRi, the trial will continue to the second stage. At stage 2, 18 additional patients will be entered. At the end of stage 2, if 17 or more patients experience complete remission, the combination will be considered worthy of further study. If ≤ 16 patients experience a complete remission, then no further investigation of the combination is warranted.

As of 12/10/2024, a total of 25 subjects have been accrued, with 23 response evaluable. Out of these 23 evaluable subjects, 17 have achieved complete remission (CR) already. Since the target success threshold 17 CR/CRi has been accomplished, and also considering the slow accrual of blinatumomab-naive patients, we are planning to accrue just one more subject and close the study. Therefore, we will end up with a total of 26 accruals, including 23-24 evaluable subjects (6 from phase 1 portion, plus 17-18 from phase 2 portion).

Endpoints:

Primary:

The primary endpoints are: toxicity (phase 1) and response (phase 2). Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events version 5. DLT is defined in section 5.3 of the protocol. Response is defined as: complete remission (CR), or CR with incomplete recovery (CRi) (according to NCCN guidelines on ALL version 1.2017 response criteria).

Secondary:

- Toxicity (phase 2)
- Time to response (CR, CRi)
- Duration of remission
- Allogeneic HSCT
- Cycles completed
- Minimal residual disease (MRD)
- Overall survival (OS)
- Event-free survival (EFS)

Sample Size:

Number of Evaluable Patients: 23-24

Phase 1: 6-12* (expected)*

Phase 2: 17-18* (expected)

*The 6 patients treated at the recommended phase 2 schedule (RP2S) in the phase 1 portion of the study will count toward the 23-24 evaluable patients required; given this, we expect to enroll only 17-18 extra evaluable patients on the phase 2 trial.

If taking into account the expected 10% inevaluable rate, the total accruals may be up to 26.

Accrual for both phases is expected to be completed in 73 months. Patients may receive up to 5 cycles of therapy and will be followed for 1 year from start of study treatment. The expected maximum follow-up/study duration is 85 months.

Estimated Duration of the Study

- Estimated Enrollment Period: 73 months (6 years)
- Patients followed for up to 1 year from start of therapy, so total study duration is 85 months, ~7 years.

Summary of Subject Eligibility Criteria:

Inclusion Criteria:

1) ≥18 years of age

2) Previously treated CD19+ ALL including Philadelphia chromosome (BCR-Abl) positive ALL that meets all of the following criteria:

a) Diagnosis of precursor B-cell ALL based on flow cytometry and histology

b) Previously treated subjects with primary refractory disease OR after first or subsequent relapse

c) Subjects with lymphoblasts in bone marrow (BM) or extramedullary disease (EMD) that is radiographically measurable and amenable to repeat biopsies

3) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.

4) Adequate organ function defined by the screening laboratory inclusion values (Table 1) and left ventricular ejection fraction (LVEF) > 45%

5) Required screening laboratory data (within 28 days prior to administration of treatment day 0) as shown in Table 1

6) Discontinuation of all anticancer therapy within 2 weeks or at least 5 half-lives (whichever is shorter) prior to study Day 1 with the following exceptions:

a) Medications that are typically part of a maintenance therapy for ALL, such as glucocorticoids, mercaptopurine, hydroxyurea, cyclophosphamide, methotrexate, vincristine or TKIs (e.g. imatinib, dasatinib) may be administered up to at least 5 half-lives or 3 days (whichever is longer) prior to the first dose.

b) Intrathecal (IT) chemotherapy may be dosed up to 7 days prior to first dose of study drug (Ara-C recommended). IT chemotherapy is allowed for CNS prophylaxis per treating physician recommendation in between cycles throughout the study.

c) Radiotherapy may be administered up to 2 weeks prior to the start of treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

d) For biologics (e.g. monoclonal antibodies), washout period of 1 month beyond the recommended dosing interval and at least 4 weeks or 5 half-lives (whichever is longer) since the last dose

7) All acute toxic effects of any prior antitumor therapy must be resolved to Grade ≤1 before enrollment, with the exception of alopecia (any grade permitted), neuropathy (≤ Grade 2) or bone marrow parameters (any grades permitted). Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use 2 protocol recommended method of contraception from the screening visit throughout the study treatment period and to 120 days from the last dose of pembrolizumab. A negative serum pregnancy test is required for female subjects at screening. Lactating females must agree to discontinue nursing before administration of pembrolizumab and 120 days post last dose.

9) For male subjects having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use 2 protocol-recommended method of contraception from the start of pembrolizumab throughout the study treatment period and for 120 days following the last dose of pembrolizumab. Also, male subjects should refrain from sperm donation from the start of pembrolizumab throughout the study treatment period and for 120 days following the last dose of pembrolizumab

10) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's ALL

11) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions. Note: psychological, social, familial or geographical factors that might preclude adequate study participation should be considered

12) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

Exclusion Criteria:

1) Diagnosis of Burkitt leukemia, mixed phenotype acute leukemia, or lymphoid blast crisis of chronic myelogenous leukemia (CML)

2) A life-threatening illness, medical condition or organ system dysfunction which, in the investigators' opinion, could compromise the subject's safety or interfere with the absorption or metabolism of pembrolizumab

3) Active or symptomatic central nervous system (CNS) disease. For study purposes, a subject will NOT be considered as having active CNS disease if the subject has documentation of prior CNS disease and has received prior treatment (IT or radiation) and is:

a) asymptomatic for the last 28 days prior to screening and

b) has documented at least 2 negative cerebrospinal fluid (CSF) cytology (which must include 1 lumbar puncture [LP] within the study screening window)

4) Uncontrolled undercurrent illness including but not limited to unstable angina pectoris or psychiatric illness/social situations that would limit compliance with study requirements. As infection is a common feature of ALL, subjects with active infection are permitted to enroll provided that the infection is documented to be under control

5) History of myelodysplastic syndrome or organ transplantation

6) History of non-lymphoid malignancy except for the following: Adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic

prostate cancer without known metastatic disease and with no requirement for therapy or requirement only hormonal therapy and with normal prostate specific antigen for > 1 year prior to the start of pembrolizumab, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment

7) Known hypersensitivity or intolerance to any of the active substance or excipients in the formulations for pembrolizumab and blinatumomab

8) Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), HIV, alcoholic liver disease, non-alcoholic steatohepatitis, cirrhosis of the liver, or portal hypertension

9) Prior allogeneic bone marrow transplantation

10) Pregnancy or breastfeeding

11) Has known history of, or any evidence of active, non-infectious pneumonitis/interstitial lung disease.

12) Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14) Is expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of pembrolizumab.

15) Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or blinatumomab.

16) Has received a live vaccine or live attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed.

17) Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of the first dose of treatment.

18) Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

Investigational Product Dosage and Administration:

Schedules A and B, up to 5 cycles of treatment allowed with the combination:

Pembrolizumab

- cycle 1: 200 mg IV day 15 for Schedule A (5-week cycle) or day 22 for Schedule B (6-week cycle)
- cycles 2 to 4: 200 mg IV days 1 and 22 each 6-week cycle

Blinatumomab 28 µg/day CIV days 1 to 28 each 6-week cycle (9 µg/day CIV on days 1 to 7 during cycle 1; cycle 1 is 5 weeks long for Schedule A)

A cycle will be defined as a 6-week period in accordance with the treatment schedule with blinatumomab based on phase 2 studies (blinatumomab given at 28 µg/day/day continuous infusion for 4 weeks with 2 weeks of treatment-free interval) with the exception of cycle 1 for Schedule A, which is a 5-week period.

During the Treatment Phase, pembrolizumab will be administered intravenously every 3 weeks and blinatumomab will be administered intravenously continuously at 9 µg/day on Day 1 of Cycle 1 through Day 7 of Cycle 1, and subsequently be given at 28 µg/day intravenously continuously on Day 8 through 28 of Cycle 1.

Clinical Observations and Tests to be Performed:

Correlative studies to be performed (collection days denoted in the study calendar in section 10):

- Composition of T cell subsets over time
- PD-1, TIM 3, and LAG1 expression over the course of treatment on subsets of T cells
- PDL1 and CD19 expression on leukemic blasts and normal B cells
- Cytokine analysis
- TCR répertoire analysis
- Leukemic cell clonality analysis
- Microbiome studies: For microbiota profiling, standard PCR methods will be required to evaluate 16SrRNA gene presence.

Statistical Considerations:

Primary Analysis Phase 1: Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, attribution, time of onset, duration, probable association with the study treatment and reversibility or outcome. Baseline information (e.g. the extent/type of prior therapy) and demographic information will be presented as well to describe the patients treated in this study.

Primary Analysis Phase 2: Overall response rate (patients that have confirmed CR/ CRi) and 95% Clopper Pearson binomial confidence interval (CI) will be calculated. In addition, sub-analyses will be performed where participants will be considered evaluable for response if they are confirmed eligible, receive at least 50% of the study treatment during the first cycle of therapy and have their disease re-evaluated. Remission rates will also be explored based on number/type of prior therapy(ies). Time to response and survival endpoints will be estimated using the product-limit method of Kaplan and Meier.

Secondary/Correlative Analyses:

Gut microbiome diversity will be estimated/assessed using the inverse Simpson index (Taur et al 2014) and the change over time (baseline, prior to pembrolizumab administration, the end of cycles 1 and 2) will be compared between responders and non-responders, or between patients of high- vs low- grade toxicities by linear mixed models. Fisher exact test will be used to assess the association between the categorized microbiome diversity (high: >4; 2-4: intermediate; low: <2) and response/toxicity. Kaplan-

Meier method and log-rank test will be used to assess the association between the baseline microbiome diversity groups and clinical outcomes (response duration, EFS/PFS and OS). Similar statistical method will be applied to the correlative studies of other biomarkers (T cell subsets, cytokines levels, PD-1/PD-L1 expressions) and clinical outcomes.
Sponsor/Licensee:
City of Hope
Research Funding:
Merck & Co. and Amgen Inc.

Abbreviations

Abbreviation	Meaning
ANC	absolute neutrophil count
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Bcr-abl	bcr-abl fusion gene
BITE	bispecific T-cell engagers
BM	bone marrow
CBC	complete blood count
CI	confidence interval
CIVI	continuous intravenous infusion
CML	chronic myelogenous leukemia
CNS	central nervous system
CR	complete remission
CRh	complete remission with partial hematological recovery
CRi	complete response incomplete recovery
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
C_{ss}	steady state drug concentration
CTCAE	Common Terminology Criteria for Adverse Event
DFS	disease-free survival
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
ECOG	eastern cooperative oncology group
eCRF	electronic case report from
Heart Rate	number of cardiac cycles per unit of time
alloHSCT	allogeneic hematopoietic stem cell transplantation
ICF	Informed consent form
ICH/GCP	international committee on harmonization/good clinical practices
IPIM	investigational product instructional manual
irAE	immune related adverse events

IRB/IEC	institutional review board/independent ethics committee
MRD	minimal residual disease
NEL	no evidence of leukemia
OS	overall survival
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PK	pharmacokinetic
R/R	relapsed/refractory
SAE	Serious adverse event
TBL	total bilirubin
TKI	tyrosine kinase inhibitor
WBC	white blood cell

1 Objectives and Hypotheses

1.1 Objectives

In adult patients with relapsed/refractory ALL:

1.1.1 Phase 1

- Assess the safety and tolerability of combination immunotherapy with blinatumomab and pembrolizumab by evaluation of toxicities including: type, frequency, severity, attribution, time course and duration (secondary objective for phase 2 portion).
- Determine the recommended phase 2 schedule (RP2S) of combination immunotherapy with pembrolizumab and blinatumomab.

1.1.2 Phase 2 (Patients on RP2S of Phase 1 included)

Primary: Estimate the anti-leukemia activity of combination immunotherapy blinatumomab and pembrolizumab as assessed by overall response rate (CR or CRi).

Secondary (all evaluable patients):

- Assess safety (Phase 2 enrollment only)
- Estimate time to response (CR or CRi) and response duration;
- Estimate overall survival and event-free survival;
- Among transplant eligible patients, determine the number and proportion of patients who bridge directly from trial therapy to allogeneic hematopoietic stem cell transplant (alloHSCT) after completing at least the first cycle of combination therapy;
- Determine the number and proportion of patients who receive single-agent blinatumomab and the proportion able to complete the full 9 cycles of blinatumomab;
- Estimate the minimal residual disease rate;

1.1.3 Correlative Studies:

- Explore evolution of T cell subsets at various points in treatment (T naïve, T effector, T effector memory, T central memory, CD4, CD8);
- Evaluate PD-L1 expression levels on ALL blasts and blast counts over time;
- Evaluate PD-1/PD-L1 expression on subsets of T cells;
- Evaluate the clonal evolution of leukemic blasts in response to treatment.
- Evaluate gut microbiome diversity in the first two cycles of treatment
- Correlation between the microbiome diversity and responses to therapy
- Correlation between microbiome diversity and toxicities, including cytokine release syndrome (CRS).

1.2 Hypotheses

- Combinational immunotherapy using pembrolizumab and blinatumomab is safe with a manageable side effect profile;
- Combinational immunotherapy using pembrolizumab and blinatumomab induces promising anti-leukemic activity compared to historical controls for blinatumomab alone.

2 Background

2.1 Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a malignant hematologic malignancy with an overall incidence of 1.1/100,000 per year. ALL has a bimodal distribution with an early peak at 4 to 5 years of age (incidence of 4.5/100,000 per year) followed by a second gradual increase at 50 years (incidence of 2/100,000 per year). This acute leukemia is marked by expansion of lymphoblasts in the bone marrow and peripheral blood, leading to arrest in normal blood cell development. The epidemiologic burden is reflected in the statistic that ALL represents 80% of acute childhood leukemia and 20% of acute leukemia cases in adults [1-3]. B-cell lineage ALL represents 75% of all adult ALL, with the remaining portion arising from T-cell lineage.

Outcomes are poor for adults with refractory or relapsed ALL. The most common treatments in adult patients with R/R B-precursor ALL include different combinations of aggressive, multi-drug chemotherapy regimens. For these patients, the goal of therapy is to induce remission and proceed to allogeneic hematopoietic stem cell transplantation (alloHSCT). Several clinical trials have shown that most subjects fail to achieve CR, with a typical CR rate of 20% to 30% [4-6]. Treatment-related mortality is high (12% to 23% of subjects); CRs are not durable (median, 4 to 5 months); and overall survival (OS) is poor (median, 4 to 6 months after relapse) [4, 5, 7].

Although alloHSCT provides a potentially curative option, it is not curative for most patients with persistent disease. Only patients in complete remission are most suitable for alloHSCT [8], and OS at 1 year is merely 17% to 28% [4, 6, 8]. In addition, morbidity and mortality from stem cell transplantation is high (20% to 30%).

It is important to differentiate the line of treatment (number of salvage treatments, number of prior relapses) as well as the duration of remission, particularly for the first remission; a longer CR predicts a higher second CR rate and an early relapse is associated with a lower second CR rate. Although alloHSCT can be performed in patients with active disease, the best outcome is observed in patients in CR; the 5-year OS estimation for patients receiving alloHSCT after second CR is 33% versus only 8% for patients receiving alloHSCT with active disease [9].

The population of interest for our study is adult patients with relapsed/refractory (R/R) B-precursor ALL. Primary refractory ALL is defined by absence of complete remission (CR) after standard induction therapy. A patient has relapsed ALL if they achieved a CR during upfront therapy (CR1) and has then relapsed during, or after continuation of therapy. Refractory relapse is defined by lack of CR after first salvage therapy. Second relapse or later relapses are defined as relapse after achieving a second complete remission (CR2) in first salvage or later salvage therapies.

2.2 Blinatumomab: Bispecific T cell engager

Blinatumomab is a member of a novel class of bispecific antibody constructs called BiTE®, or “bispecific T-cell engagers” [10]. It is an antibody construct with dual binding specificities. T cells are bound by its anti-CD3 moiety, whereas B lymphoblasts and cells are bound by the anti-CD19 moiety. This unique feature of blinatumomab allows it to transiently connect malignant cells with T cells, thereby inducing T-cell mediated killing of the bound malignant cell [11, 12]. In preclinical models, blinatumomab-mediated T-cell activation involves the transient release of inflammatory cytokines and proliferation of T cells. The subsequent serial lysis of multiple malignant cells by a single blinatumomab-activated T cell closely resembles a natural cytotoxic T-cell reaction.

Blinatumomab was developed by genetic engineering from 2 distinct parental murine monoclonal antibodies (mAbs): HD37, which recognizes the pan-B cell antigen CD19; and L2K-07, which specifically

binds the T-cell receptor (TCR)-associated complex, CD3. The single-chain variable fragments (scFv) of these antibodies are linked to form 1 single polypeptide chain.

As described above, blinatumomab specifically targets cells that express CD19, a marker solely expressed by B cells, including B-precursor ALL cells, with an affinity of 1.6×10^{-9} M. Blinatumomab recruits and activates T cells via a lower affinity interaction with CD3 (8.7×10^{-8} M). These activated T cells then induce a half-maximal target cell lysis ranging in vitro between 10 to 100 pg/mL showing blinatumomab to be an extremely potent molecule [10].

During the course of tumor cell elimination, activated T cells synthesize and secrete pro-inflammatory cytokines, which might induce symptoms as fever or decreases of blood pressure. In vitro data demonstrate cytokine release as a result of blinatumomab-mediated activation, which can be attenuated by corticosteroids without impairing the cytotoxic activity. In vivo data indicate cytokine release to be most prominent following the first dose of blinatumomab.

Due to its unique ability to redirect T cells via CD3 toward a CD19+ tumor cell lysis, blinatumomab can elicit repeated target cell elimination by cytotoxic T cells and a polyclonal response of previously primed CD4+ and C8+ T cells. The antitumor activity is effective within a wide range of effector to target ratios. In the absence of CD19+ target cells neither cytotoxicity nor release of cytokines will occur. Blinatumomab acts strictly in a target cell-specific and T-cell dependent manner, with regard to cytotoxic action. The presence of both, CD19+ target cells and T cells are required for its cytotoxic activity.

Please refer to Blinatumomab Investigator's Brochure for full preclinical details [13].

2.2.1 Clinical Efficacy of Blinatumomab

The safety and efficacy of blinatumomab were evaluated in an open-label, multicenter, single-arm study of 189 patients Ph-negative R/R B-precursor ALL. These patients were ≥ 18 years of age with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL (relapsed with first remission duration of ≤ 12 months in first salvage or relapsed or refractory after first salvage therapy or relapsed within 12 months of alloHSCT, and had ≥ 10% blasts in bone marrow).

Blinatumomab was administered as a continuous intravenous infusion. In the first cycle, the initial dose was 9 µg/day for week 1, then 28 µg/day for the remaining 3 weeks. In this study population, the median age was 39 years (range: 18 to 79 years), 63 out of 185 (34.1%) had undergone alloHSCT prior to receiving blinatumomab, and 32 out of 185 (17.3%) had received more than 2 prior salvage therapies.

The primary endpoint was the complete remission/complete remission with partial hematological recovery (CR/CRh) rate within 2 cycles of treatment. Seventy-seven out of 185 (41.6%) evaluable patients achieved CR/CRh* within the first 2 treatment cycles, with the majority of responses (81%, 62 out of 77) occurring within cycle 1 of treatment. The alloHSCT rate among those who achieved CR/CRh was 39% (30 out of 77) [13-15].

Recently, the randomized phase 3 trial by Kantarjian et al. of blinatumomab (271 patients) versus chemotherapy (134) demonstrated a CR rate of 34% and an overall response rate (CR+CRh+CRi) of 44% [16]. Overall survival was significantly longer in the blinatumomab vs chemotherapy arms. Median overall survival was 7.7 months in the blinatumomab vs 4.0 months in the chemotherapy arm (hazard ratio for death with blinatumomab vs. chemotherapy, 0.71; 95% confidence interval [CI], 0.55 to 0.93; P=0.01). Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab are vs the chemotherapy group, both with respect to complete remission with full hematologic recovery (34% vs. 16%, P<0.001) and with respect to complete remission with full, partial, or incomplete hematologic recovery (44% vs. 25%, P<0.001).

2.2.2 Clinical Safety of Blinatumomab

The safety data described in this section is obtained via cumulative experience in clinical trials in which 212 patients with relapsed or refractory ALL received up to 28 μg/day, as also described in blinatumomab package insert [14]. All patients received at least one dose. The median age of the study population was 37 years (range: 18 to 79 years), 63% were male, 79% were White, 3% were Asian, and 3% were Black or African American.

The most common adverse reactions (≥ 20%) were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), and constipation (20%).

Serious adverse reactions were reported in 65% of patients. The most common serious adverse reactions (≥ 2%) included febrile neutropenia, pyrexia, pneumonia, sepsis, neutropenia, device-related infection, tremor, encephalopathy, infection, overdose, confusion, Staphylococcal bacteremia, and headache.

Adverse reactions of Grade 3 or higher were reported in 80% of patients. Discontinuation of therapy due to adverse reactions occurred in 18% of patients treated with blinatumomab. The adverse reactions reported most frequently as the reason for discontinuation of treatment included encephalopathy and sepsis. Fatal adverse events occurred in 15% of patients. The majority of these events were infections. No fatal adverse events occurred on treatment among patients in remission.

The blinatumomab (BLINCYTO®) full prescribing information also includes the following safety warnings:

- Cytokine Release Syndrome (CRS), which may be life-threatening or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. The median time to onset of CRS was 2 days after the start of infusion and the median time to resolution of CRS was 5 days among cases that resolved. Manifestations of CRS include fever, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin, and disseminated intravascular coagulation (DIC). The manifestations of CRS after treatment with BLINCYTO overlap with those of infusion reactions, capillary leak syndrome (CLS), and hemophagocytic histiocytosis/macrophage activation syndrome (MAS). Using all of these terms to define CRS in clinical trials of BLINCYTO, CRS was reported in 15% of patients with relapsed or refractory ALL and in 7% of patients with MRD-positive ALL. Monitor patients for signs or symptoms of these events. Advise outpatients on BLINCYTO to contact their healthcare professional for signs and symptoms associated with CRS. If severe CRS occurs, interrupt BLINCYTO until CRS resolves. Discontinue BLINCYTO permanently if life-threatening CRS occurs. Administer corticosteroids for severe or life-threatening CRS.
- Neurological toxicities, which may be severe, life-threatening, or fatal, occurred in patients receiving BLINCYTO. Interrupt or discontinue BLINCYTO as recommended. In patients with ALL receiving BLINCYTO in clinical studies, neurological toxicities have occurred in approximately 65% of patients. Among patients that experienced a neurologic event, the median time to the first event was within the first 2 weeks of BLINCYTO treatment and the majority of events resolved. The most common (≥ 10%) manifestations of neurological toxicity were headache, and tremor; the neurological toxicity profile varied by age group. Grade 3 or higher (severe, life-threatening, or fatal) neurological toxicities following initiation of BLINCYTO administration occurred in approximately 13% of patients and included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Manifestations of neurological toxicity included cranial nerve disorders. The majority of neurologic events resolved following interruption of BLINCYTO, but some resulted in treatment discontinuation. There is limited experience with BLINCYTO in patients with active

ALL in the central nervous system (CNS) or a history of neurologic events. Patients with a history or presence of clinically relevant CNS pathology were excluded from clinical studies. Monitor patients receiving BLINCYTO for signs and symptoms of neurological toxicities. Advise outpatients on BLINCYTO to contact their healthcare professional if they develop signs or symptoms of neurological toxicities.

- Infections: In patients with ALL receiving BLINCYTO in clinical studies, serious infections such as sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections were observed in approximately 25% of patients, some of which were life-threatening or fatal. As appropriate, administer prophylactic antibiotics and employ surveillance testing during treatment with BLINCYTO. Monitor patients for signs and symptoms of infection and treat appropriately.
- Tumor lysis syndrome (TLS), which may be life-threatening or fatal, has been observed in patients receiving BLINCYTO. Appropriate prophylactic measures, including pretreatment nontoxic cytoreduction and on-treatment hydration, should be used for the prevention of TLS during BLINCYTO treatment. Monitor for signs or symptoms of TLS. Management of these events may require either temporary interruption or discontinuation of BLINCYTO.
- Neutropenia and febrile neutropenia, including life-threatening cases, have been observed in patients receiving BLINCYTO. Monitor laboratory parameters (including, but not limited to, white blood cell count and absolute neutrophil count) during BLINCYTO infusion. Interrupt BLINCYTO if prolonged neutropenia occurs.
- Effects on Ability to Drive and Use Machines: Due to the potential for neurologic events, including seizures, patients receiving BLINCYTO are at risk for loss of consciousness. Advise patients to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while BLINCYTO is being administered.
- Elevated liver enzymes: Treatment with BLINCYTO was associated with transient elevations in liver enzymes. In patients with ALL receiving BLINCYTO in clinical studies, the median time to onset of elevated liver enzymes was 3 days. The majority of these transient elevations in liver enzymes were observed in the setting of CRS. For the events that were observed outside the setting of CRS, the median time to onset was 19 days. Grade 3 or greater elevations in liver enzymes occurred in approximately 7% of patients outside the setting of CRS and resulted in treatment discontinuation in less than 1% of patients. Monitor alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during BLINCYTO treatment. Interrupt BLINCYTO if the transaminases rise to greater than 5 times the upper limit of normal or if total bilirubin rises to more than 3 times the upper limit of normal.
- Pancreatitis: Fatal pancreatitis has been reported in patients receiving BLINCYTO in combination with dexamethasone in clinical studies and the postmarketing setting. Evaluate patients who develop signs and symptoms of pancreatitis. Management of pancreatitis may require either temporary interruption or discontinuation of BLINCYTO and dexamethasone.
- Leukoencephalopathy: Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed in patients receiving BLINCYTO, especially in patients with prior treatment with cranial irradiation and antileukemic chemotherapy (including systemic high-dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.
- Immunization: The safety of immunization with live viral vaccines during or following BLINCYTO therapy has not been studied. Vaccination with live virus vaccines is not recommended for at least 2 weeks prior to the start of BLINCYTO treatment, during treatment, and until immune recovery following last cycle of BLINCYTO.

Relapse of CD19 negative B-precursor ALL and lineage switch from ALL to AML have been observed in patients with ALL, during or following blinatumomab treatment, in clinical trials and the post marketing setting.

2.3 **Pembrolizumab (MK-3475)**

2.3.1 Anti-PD1 and Immunotherapy in Malignancy

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades [17]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [18, 19].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [20, 21]. The structure of murine PD-1 has been resolved [22]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [21, 23-25]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [26, 27]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B cells, T regs, and natural killer cells [28, 29]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells [30]. The ligands for PD-1, programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2) are constitutively expressed or can be induced in a variety of cell types including nonhematopoietic tissues and in various tumors [17, 27, 31, 32]. Both ligands are type 1 transmembrane receptors containing IgV-like and Ig constant–like (IgC-like) domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [27]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma [33], pancreatic carcinoma [34], hepatocellular carcinoma [35], and ovarian carcinoma [36]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [37]. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-

1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

2.3.2 Nonclinical Pharmacology

Pembrolizumab is a highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region. The theoretical molecular weights of the heavy and light chains derived from the amino acid sequences, excluding glycosylation, are 49.4 kiloDaltons (KDa) and 23.7 KDa, respectively. The antibody is heterogeneously glycosylated at asparagine 297 within the Fc domain of each heavy chain, yielding molecular weights typically ranging between 148.9 and 149.5 KDa, depending on the attached glycan chains.

Pembrolizumab potently blocks binding to both ligands (PD-L1 and PD-L2) with half maximal inhibitory concentration (IC50) values below 1 nanomolar (nM). Pembrolizumab binds to human and cynomolgus monkey PD-1 with comparable affinity and blocks the binding of human and cynomolgus monkey PD-1 to PDL1 and PD-L2 with comparable potency. Pembrolizumab does not cross-react with dog, rat, or mouse PD-1.

Pembrolizumab enhances T-cell responses in human donor blood cell cultures, with a half-maximal effective concentration (EC50) of approximately 0.1 to 0.3 nM. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and cynomolgus monkeys. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T-cells.

Pembrolizumab does not bind immunoglobulin superfamily members CD28, CTLA-4, or inducible T-cell co-stimulator (ICOS). In in vitro peripheral blood mononuclear cell (PBMC) and whole blood cytokine release assays, the cytokine levels induced by pembrolizumab were low and comparable to those induced by trastuzumab. Pembrolizumab does not induce ADCC or CDC.

Using an anti–mouse PD-1 surrogate antibody J43, PD-1 blockade is demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti–PD-1 therapy enhances the effect of chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased efficacy and increased complete regression rates in vivo. The results of studies conducted in a syngeneic mouse model of renal carcinoma revealed that immunosuppressive doses of dexamethasone included in standard-of-care treatment for NSCLC do not reduce the antitumor efficacy of muDX400, another anti-mouse PD-1 surrogate antibody. Moreover, the antitumor efficacy of combination treatment with muDX400 and certain standard of care for NSCLC is greater than that of standard of care alone. In some combinations, complete tumor regressions were observed.

Please refer to pembrolizumab investigator brochure for full details [38].

2.3.3 Summary of Human Pharmacokinetics

The dose of pembrolizumab in this trial is 200 mg every 3 weeks (Q3W). The dose recently approved in the United States for treatment of melanoma patients is 2 mg/kg Q3W. Recent studies in other tumor types have indicated that 10 mg/kg Q2W and 200 mg Q3W are likely to be similar with regard to efficacy and tolerability.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of Protocol 001 evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors [15]. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-

human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date.

Pharmacokinetic (PK) data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to the IB). Pharmacodynamic (PD) data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days. A population PK analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights.

Pembrolizumab has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight-based regimen are anticipated to remain well within the established exposure margins of 0.5-5.0 for pembrolizumab in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W versus the proposed dose regimen of 2 mg/kg Q3W (i.e., 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the Non-small-cell lung carcinoma (N SCLC) and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that: 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks; 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response; and 3) will maintain individual patients exposure in the exposure range established in melanoma patients that are well tolerated and safe.

Specific Populations: The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The CL of pembrolizumab increased with increasing body weight; the resulting exposure differences were adequately addressed by the administration of a weight-based dose. The following factors had no clinically important effect on the CL of pembrolizumab: age (range 18-94 years), gender, renal impairment, mild hepatic impairment, and tumor burden. The effect of race could not be assessed due to limited data available in non-White patients.

Renal Impairment: The effect of renal impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=210), moderate (eGFR 30 to 59 mL/min/1.73m2; n=43), or severe (eGFR 15 to 29 mL/min/1.73m2; n=2) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73m2; n=221) renal function. No clinically important differences in the CL of pembrolizumab were found between patients with renal impairment and patients with normal renal function.

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Hepatic Impairment: The effect of hepatic impairment on the CL of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (TB less than or equal to ULN and AST greater than ULN or TB between 1 and 1.5 times ULN and any AST; n=59) compared to patients with normal hepatic function (TB and AST less than or equal to ULN; n=410). No clinically important differences in the CL of pembrolizumab were found between patients with mild hepatic

impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe (TB greater than 3 times ULN and any AST) hepatic impairment.

Please refer to pembrolizumab investigator brochure [38] and package insert [39] for full details.

2.3.4 Toxicology, carcinogenesis, mutagenesis, and impairment of fertility

In the 1-month and 6-month toxicology study in cynomolgus monkeys, pembrolizumab administered once a week and once every other week respectively, intravenously up to 200 mg/kg resulted in no adverse treatment related effects. The exposure multiple based on a predicted AUC0-tau of 4464 μg·day/mL at the maximum anticipated human clinical dose of 10 mg/kg Q2W or Q3W is 15-fold at 200 mg/kg, the no observed adverse effect level for the 6-month monkey study. Additionally, the tissue cross-reactivity study of pembrolizumab with human and monkey tissues demonstrated the expected on-target staining of the membranes of mononuclear leukocytes in both species. Off-target cross-reactivity staining was also noted in both species but was limited to cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix), and was considered related to the experimental method artifacts, i.e. tissue processing for IHC, that are well-recognized limitations of tissue cross-reactivity studies and, thus not considered toxicologically relevant.

No studies have been performed to test the potential of pembrolizumab for carcinogenicity or genotoxicity. Fertility studies have not been conducted with pembrolizumab. In 1-month and 6-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature. Therefore, inclusion of women of childbearing potential in clinical trials should be in accordance with the study protocol and applicable regulatory guidance (e.g., ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals).

2.3.5 Summary of Clinical Safety of Pembrolizumab

In the pembrolizumab monotherapy trials, the overall incidence of AEs ranged from 83.0% to 100%. The most commonly reported AEs included fatigue, diarrhea, decreased appetite, nausea, and anemia. The incidence of drug –related AEs (DRAEs) ranged from 39.8% to 80.0%. The most commonly reported DRAEs across all studies were nausea, fatigue, and diarrhea. The incidence of Grade 3-5 DRAEs across studies ranged from 6.8% to 12.0%. The most commonly reported Grade 3-5 DRAEs were anemia, alanine aminotransferase increased, and aspartate aminotransferase increased. Most subjects who experienced an AE continued in the study, with the incidence of AEs leading to discontinuation ranging from 1.9% to 12.3%. The majority of AEs leading to discontinuation were not considered drug related. Discontinuations due to a DRAE were infrequent and ranged from 0% (no subjects in P011) to 4.5% (4 of 88 subjects in P013). The most commonly reported DRAEs leading to discontinuation were pneumonitis, alanine aminotransferase increased, and aspartate aminotransferase increased.

The overall pattern of AEs observed in melanoma subjects demonstrates favorable safety profile when this immune therapy is compared to chemotherapy. Consistent with prior observations from randomized comparisons of the 2 mg/kg and 10 mg/kg dose levels when given every 3 weeks, there are no important differences in the safety profile of pembrolizumab at these 2 dose levels, and both doses appear to have a favorable safety profile compared to chemotherapy.

In the combination therapy trials (combination with chemotherapy in lung cancer and combination with lenalidomide and dexamethasone in myeloma), the overall incidence of AE’s was 95.4% when combined with chemotherapy in lung cancer and 80% in combination with lenalidomide and dexamethasone. Due to the fact that these trials were combination studies, and also because of the small sample size, comparative

evaluation of the AE profile of pembrolizumab combination therapy from those protocols to pembrolizumab monotherapy or to chemotherapy monotherapy in other studies cannot be made.

Among the early phase 1 study of pembrolizumab for lung, melanoma and advanced/metastatic tumors, the incidence of adverse events of special interest (AEOSI) was 16.1%. Overall, the most commonly reported AEOSI included hypothyroidism (7.2% of subjects), pneumonitis (2.9% of subjects), infusion reaction (2.5% of subjects), and hyperthyroidism (2.2% of subjects). The incidences of the remaining AEOSI were low (range of 0.1 to 1.3% of subjects). The overall incidence of drug-related AEOSI was 14.3%. Overall, 2.6% of subjects discontinued treatment due to an AEOSI and the most commonly reported drug related AEOSI leading to discontinuation was pneumonitis (1.3% of subjects). Only one subject died of AEOSI (pneumonitis, 0.1% of subjects). No corticosteroids were used to manage myositis, pericarditis, thyroiditis, type 1 diabetes mellitus, uveitis and vasculitis.

2.3.5.1 Safety update from pembrolizumab (KEYTRUDA®) full prescribing information dated January, 2023 and IB version 23 dated October, 2022

The pembrolizumab (KEYTRUDA®) Investigator's Brochure (IB) version 25 dated October 10, 2024 [38] describes the safety of pembrolizumab as evaluated in 2799 patients in controlled and uncontrolled studies (KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010). The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year. Pembrolizumab was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving pembrolizumab. Of these treatment-related SAEs, the most common were pneumonitis, colitis, diarrhea, and pyrexia.

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving pembrolizumab in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Immune-mediated adverse reactions (ARs), including severe and fatal cases, have occurred in patients receiving pembrolizumab. Immune-mediated ARs can occur after discontinuation of treatment. Immune-mediated ARs affecting more than one body system can occur simultaneously. In clinical studies, most immune-mediated ARs were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids, and/or supportive care.

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with pembrolizumab in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis and vasculitis and hypoparathyroidism. The following was reported in other clinical studies with pembrolizumab or in postmarketing use: myocarditis and sclerosing cholangitis.

The safety profile for pembrolizumab also includes 2 important potential risks – ie, increased risk of severe complications (such as early severe graft-versus-host disease (GVHD) and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors; and GVHD after pembrolizumab administration in patients with a history of allogeneic HSCT.

The pembrolizumab (KEYTRUDA®) prescribing information dated January, 2023 includes the following safety warnings (see **Table 5** for dose modifications) [39]:

- Immune-mediated pneumonitis (including fatal cases): Monitor patients for signs and symptoms of pneumonitis.
- Immune-mediated colitis: Monitor patients for signs and symptoms of colitis.

- Immune-mediated hepatitis (including autoimmune hepatitis): Monitor patients for changes in liver function.
- Immune-mediated endocrinopathies:
  - Adrenal insufficiency: monitor for adrenal insufficiency.
  - Hypophysitis: Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
  - Thyroid disorders: Monitor for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - Type 1 diabetes mellitus, including diabetic ketoacidosis: Monitor patients for hyperglycemia and other signs and symptoms of diabetes.
- Immune-mediated nephritis, including autoimmune nephritis and interstitial nephritis with renal failure: Monitor patients for changes in renal function.
- Immune-mediated skin adverse reactions including, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some with fatal outcome): Monitor for signs or symptoms of SJS or TEN.
- Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received pembrolizumab or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.
  - Cardiac/Vascular: Myocarditis, pericarditis, vasculitis
  - Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy, optic neuritis.
  - Ocular: Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Haradalike syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.
  - Gastrointestinal: Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis, exocrine pancreatic insufficiency
  - Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica
  - Endocrine: Hypoparathyroidism
  - Hematologic/Immune: Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

- Infusion-related reactions: Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving pembrolizumab.

2.3.6 Clinical Trials of Pembrolizumab and other Anti-PD-1 Immunotherapy

Pembrolizumab monotherapy and in combination with chemotherapy have been administered to thousands of subjects with solid tumors in numerous Phase I, II, and III clinical trials sponsored by Merck. The anti-PD-1 antibody has demonstrated remarkable antitumor activity across these solid malignancies, most notably in melanoma and non-small cell lung cancer. In general the overall response rates for

pembrolizumab treatment compared favorably to historical response rates for available treatments for melanoma, particularly in subjects who had progressed after multiple prior therapies.

Moreover, anti-PD-1 immunotherapy is being explored in hematologic malignancies and results have been promising. The use of nivolumab in relapsed or refractory classical Hodgkin lymphoma (cHL) has demonstrated substantial therapeutic activity and acceptable safety profile. An objective response was reported in 20 patients (87%), including 17% with a complete response and 70% with a partial response; the remaining 3 patients (13%) had stable disease [40].

More recently, in the ongoing phase 1b trial KEYNOTE-013, treatment with pembrolizumab generated responses in 66% of patients with heavily pretreated cHL, based on preliminary data reported at the 56th Annual Meeting of the American Society of Hematology (ASH) [41]. Of the 29 evaluable patients with cHL who received pembrolizumab, six patients (21%) experienced complete remission while 13 patients (45%) achieved a partial remission. The median duration of response has not been reached. Additionally, pembrolizumab was extremely well tolerated; the most commonly reported adverse events were grade 1-2 respiratory events (20%) and thyroid disorders (20%).

Other (unpublished) avenues of discovery for the role of anti-PD-1 immunotherapy have now included a broad range of hematologic malignancies – including myeloma, myelodysplastic syndrome, and leukemias. NCT02767934 is an ongoing trial of single-agent pembrolizumab for patients with ALL with MRD after therapy (initial or salvage). In a personal communication, Dr. Ryan Cassaday, the PI of NCT02767934 informed us that in the first 8-9 patients treated, they have seen no evidence of activity from monotherapy with pembrolizumab as no one has had a reduction in their level of MRD after treatment. Pembrolizumab was tolerated very well with only a couple of mild immunologic events (pruritus and infusion reaction, respectively) and 1 patient that went quickly to allo transplant afterward and developed hyperacute GVHD (possibly related to pembrolizumab).

2.4 Rationale for Pembrolizumab and Blinatumomab Combination Immunotherapy

As described above, modern multi-agent chemotherapy regimens have increased the cure rate of ALL but at the expense of significant toxicity. Moreover, in persistent and relapse/recurrent disease, outcome is dismal with median overall survival of four to six months in adult patients. In this setting, allogeneic stem cell transplantation has historically provided 40% long term remission if a second remission is achieved.

However, second remission is often difficult to achieve with conventional chemotherapy. Such novel agents as blinatumomab have provided impressive efficacy in this niche. As monotherapy, blinatumomab immunotherapy has led to 41.6% CR/Cri in patients with relapsed/refractory ALL as described above. Yet, there is still much to explore in the way of augmenting the therapeutic efficacy of blinatumomab.

One such exploratory avenue of augmenting efficacy of blinatumomab is to exploit the PD-1/PD-L1 pathway in acute leukemia. The recent identification that increasing percentage or amount of regulatory T cells (Tregs) prior to blinatumomab therapy may predict response in R/R ALL patients is critical to this end [42]. In their analysis of 31 R/R ALL patients, those who were refractory to the treatment had a median of 16.1% (8.4-73%) Tregs, whereas responders had median of 8.55% Tregs (3.8-14.2%) (p value: 0.00013). They subsequently reported upregulation of CD69, CD25 and PD-1 on regulatory T cells incubated with blinatumomab and primary ALL blasts, suggesting a potential role of immune inhibitory molecules such as PD-1 in the resistance to blinatumomab.

As described above, the PD-1/PD-L1 pathway has been shown to directly regulate the development, maintenance, and function of Treg cells. More importantly, this pathway has been shown to directly regulate the extent of cytolytic T cell function. Blocking PD-1/PD-L1 pathway using anti-PD1 antibodies has translated into overall survival benefit in patients with advanced melanoma, NSCLC and other solid and now hematologic malignancies. Consequently, we postulate that blocking the PD-1/PD-L1 pathway using

pembrolizumab can be safely combined with blinatumomab to augment the therapeutic efficacy of blinatumomab in the treatment of patients with relapsed/refractory ALL and potentially serve as a bridge to alloHSCT.

2.5 **Rationale for Dosing Schedules**

Schedule A begins patients on blinatumomab at 9 μg/kg for the first 7 days of treatment, steps up to 28 μg/kg of blinatumomab on day 8, and then adds pembrolizumab 7 days later on day 15. Since PD-1 upregulation has been observed during blinatumomab treatment and two-thirds of blinatumomab responses occur in cycle 1, we wanted to begin pembrolizumab as early as possible in cycle 1. We felt that in the first cycle, pembrolizumab should not be added until 7 days after the blinatumomab step to 28 μg/kg, to allow separation of toxicity attributions. Thus, the first possible dosing for pembrolizumab was day 15 in Schedule A. To maintain a 21-day dosing interval for pembrolizumab, the first cycle Schedule A must end at day 35 (cycles 2-4 are 42 days), shortening the treatment-free interval for blinatumomab to 7 days for that first cycle. However, Amgen (blinatumomab sponsor) did not object to decreasing the rest period to 7 days for the first cycle to accommodate the pembrolizumab 21-day schedule.

Schedule B will be opened only if Schedule A is too toxic (1 DLT in 3 patients or 2 DLTs in 6 patients), and is the same except that pembrolizumab does not start until day 22 of cycle 1, and the cycle length for cycle 1 is 42 days (the same as for cycles 2-4). Schedule B is intended to give one additional week for patients to adjust to initial blinatumomab toxicity prior to starting pembrolizumab in the first cycle. If after 21 days on blinatumomab, pembrolizumab cannot be safely added, we must assume that the two drugs are not compatible for co-administration.

3 Patient Eligibility

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

3.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1) ≥18 years of age

2) Previously treated ALL including Philadelphia chromosome (BCR-Abl) positive ALL who meet all of the following criteria:

a) Diagnosis of CD19-positive B-cell ALL based on flow cytometry and histology

b) Previously treated subjects with primary refractory disease OR after first or subsequent relapse

c) Subjects with detectable lymphoblasts in bone marrow (BM) or extramedullary disease (EMD) that is radiographically measurable and amenable to repeat biopsies

3) Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (**Appendix 18.1**)

4) Adequate organ function defined by the screening laboratory inclusion values (Table 1)

Table 1. Adequate Organ Function Laboratory Values

System	**Laboratory Value**
Cardiac	
Left ventricular ejection fraction (LVEF)	>45%
Pulmonary	
Pulmonary Function Tests	DLCO (adjusted for hemoglobin) > 50% predicted
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Pregnancy	
βHCG	negative
Infection	
HIV	Negative HIV antibody/PCR
HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative HBV DNA by quantitative PCR
HCV	Negative viral RNA (if HCV antibody is positive

5) Required screening laboratory data (within 28 days prior to treatment day 0) as shown in **Table 1**)

6) Discontinuation of all anticancer therapy within 2 weeks or at least 5 half-lives (whichever is shorter) prior to study Day 1 with the following exceptions:

a) Medications that are typically part of a maintenance therapy for ALL, such as glucocorticoids, mercaptopurine, hydroxyurea, cyclophosphamide, methotrexate, vincristine or TKIs (e.g. imatinib, dasatinib) may be administered up to at least 5 half-lives or 3 days (whichever is longer) prior to the first dose.

b) Intrathecal (IT) chemotherapy may be dosed up to 7 days prior to first dose of study drug (Ara-C recommended). IT chemotherapy is allowed for CNS prophylaxis per treating physician recommendation in between cycles throughout the study.

c) Radiotherapy may be administered up to 2 weeks prior to the start of treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

d) For biologics (e.g. monoclonal antibodies), washout period of 1 month beyond the recommended dosing interval and at least 4 weeks or 5 half-lives (whichever is longer) since the last dose

7) All acute toxic effects of any prior antitumor therapy must be resolved to Grade ≤1 before enrollment, with the exception of alopecia (any grade permitted), neuropathy (≤ Grade 2) or bone marrow parameters (any grades permitted). Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

8) For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use 2 concurrent protocol recommended methods of contraception (listed in Section 5.7) from the screening visit throughout the study treatment period and to 120 days from the last dose of pembrolizumab. A negative serum pregnancy test is required for female subjects at screening. Lactating females must agree to discontinue nursing before administration of study drugs and 120 days post last dose of pembrolizumab.

9) For male subjects having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use 2 protocol-recommended methods of contraception (listed in Section 5.7) from the start of study throughout the study treatment period and for 120 days following the last dose of pembrolizumab. Also, male subjects should refrain from sperm donation from the start of pembrolizumab throughout the study treatment period and for 120 days following the last dose of pembrolizumab.

10) In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's ALL

11) Willingness to comply with scheduled visits, drug administration plan, imaging studies, laboratory tests, other study procedures, and study restrictions. Note: psychological, social, familial or geographical factors that might preclude adequate study participation should be considered

12) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

3.2 **Exclusion Criteria**

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study

1) Diagnosis of mature B-cell ALL (Burkitt's leukemia) or mixed phenotype acute leukemia according to WHO classification, or lymphoid blast crisis of chronic myelogenous leukemia (CML)

2) A life-threatening illness, medical condition or organ system dysfunction which, in the investigators' opinion, could compromise the subject's safety or interfere with the absorption or metabolism of pembrolizumab

3) Active or symptomatic central nervous system (CNS) disease

- For study purposes, a subject will NOT be considered as having active CNS disease if the subject has documentation of prior CNS disease and has received prior treatment (IT or radiation) and is:

a) asymptomatic for the last 28 days prior to screening and

b) has documented at least 2 negative cerebrospinal fluid (CSF) cytology (which must include 1 lumbar puncture [LP] within the study screening window)

4) Uncontrolled undercurrent illness including but not limited to unstable angina pectoris or psychiatric illness/social situations that would limit compliance with study requirements. As infection is a common feature of ALL, subjects with active infection are permitted to enroll provided that the infection is documented to be under control

5) History of myelodysplastic syndrome or organ transplantation

6) History of non-lymphoid malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requirement only hormonal therapy and with normal prostate specific antigen for > 1 year prior to the start of pembrolizumab, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment

7) Known hypersensitivity or intolerance to any of the active substance or excipients in the formulations for pembrolizumab and blinatumomab

8) Ongoing drug-induced liver injury, chronic active hepatitis C (HCV), chronic active hepatitis B (HBV), HIV, alcoholic liver disease, non-alcoholic steatohepatitis, cirrhosis of the liver, or portal hypertension

9) Prior allogeneic bone marrow transplantation

10) Pregnancy or breastfeeding

11) Has known history of, or any evidence of active, non-infectious pneumonitis/interstitial lung disease

12) Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

13) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14) Is expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of pembrolizumab.

15) Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or blinatumomab.

16) Has received a live vaccine or live attenuated vaccine within 30 days of planned start of study therapy. Administration of killed vaccines is allowed. Note: please refer to **Section 5.6.3** for information on COVID-19 vaccines

17) Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of the first dose of treatment.

18) Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____ _			
*Eligibility should be confirmed per institutional policies.			

4 Participant Enrollment

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see **Section 16.5**), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in **Section 10.0**.

4.2 Participant Enrollment

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope. DCC staff are available between the hours of 8:00 a.m. and 5:00 p.m. PST, Monday through Friday (except holidays). DCC contact information is as follows:

- E-mail: DCC@coh.org

4.3 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.4 Registration Process

Allow up to 24 hours for the DCC to review. To register a participant, the subsequent procedure must be followed.

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
   - Registration Cover Sheet (**Appendix 18.2**)
   - Completed Eligibility Criteria List (printed from **Section 3.0** of the protocol) with required signature(s)
   - Signed informed consent
   - Signed HIPAA authorization form (if separate from the informed consent document)
   - Signed subject's Bill of Rights
3. In some cases, the DCC may request additional documentation prior to registration. Please refer to the Work Instruction – Reviewing Registration Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.

4. When all documents are received, the DCC will review and work with the study team to resolve any missing elements. Any missing documents may delay registration. A participant failing to meet all requirements will not be registered and the study team will be immediately notified.
5. The DCC will send a Confirmation of Registration Form, including the Subject Study Number and cohort assignment to:
   - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC and pharmacy (as needed).
   - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
6. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

4.5 Screen Failures and Registered Participants Who Do Not Begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (**Appendix 18.2**) and submitted to the DCC.

Issues that would cause treatment delays should be discussed with the Study PI.

5 Treatment Program

5.1 Study Design Overview

This study will be conducted as a single center, open-label, phase 1/2 clinical trial.

The study is designed to evaluate the safety and anti-leukemia activity of pembrolizumab when combined with blinatumomab as part of a 5 or 6-week treatment cycle (Schedule A or B). The anti-leukemia activity of the combination therapy, among patients treated at the recommended phase 2 schedule, will also be assessed. The pembrolizumab (200mg) and blinatumomab doses (28 µg/day) are fixed except that blinatumomab is given at 9 µg/day on days 1 to 7 during cycle 1. Patients are expected to receive at least the first cycle of combination therapy. If safe and tolerable, patients may receive up to 5 cycles of combination treatment. Patients, who achieve CR or CRi in response to combination therapy, may switch to single agent blinatumomab for up to 4 cycles or bridge to alloHSCT. Note: As part of single agent or combination therapy, patients may not receive more than a total of 9 cycles of blinatumomab.

5.1.1 Phase 1:

The phase 1 portion of the trial will implement traditional '3+3 rules', for enrollment schedule 'reduction' (from Schedule A to Schedule B), or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs) during cycle 1. Up to two schedules will be tested.

Schedule[+]	**Cycle Length**	**Pembrolizumab: 200mg**	**Blinatumomab: 28 µg/day† CIV**
A (starting schedule)	35 days cycle 1, 42 days cycles 2–5	cycle 1[#]: day 15 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28
B*	42 days all cycles	cycle 1: day 22 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28

+: Enrolled patients may receive up to 5 cycles of treatment.
*: While it is believed that Schedule A will be well tolerated, one schedule 'reduction' is allowed, from Schedule A to Schedule B, in the presence of dose limiting toxicity. Under Schedule B, during cycle 1, initiation of pembrolizumab is delayed by 7 days and the treatment free interval is extended to 14 days.
#: The length of cycle 1 in Schedule A is 35 days. All other cycles in Schedules A and B are 42 days.
†: In cycle 1, on days 1-7, blinatumomab will be given at 9 µg/day

Depending on schedule assignment, the first cycle will be either 35 days (Schedule A) or 42 days (Schedule B). As part of the planned therapy, patients will be treated for up to 5 cycles of combination therapy, +/- 4 additional cycles of single agent blinatumomab, disease relapse, progression, unacceptable toxicity, start of alloHSCT conditioning, or other criteria for removal from study treatment are satisfied. Patients will undergo response evaluation using the NCCN ALL response criteria v01.2017 at the end of each cycle of treatment.

The schedule that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated schedule. The recommended phase 2 schedule of pembrolizumab/blinatumomab will generally be the same as the maximum tolerated schedule, but it may be less than the maximum tolerated schedule based on a review of available data/cumulative toxicities. Once the maximum tolerated schedule/ recommended phase 2 schedule has been determined the phase 2 study of the combination will be initiated.

5.1.2 Phase 2:

The phase 2 portion will implement a Simon two-stage optimal design (Simon 1989; Jung 2004) to evaluate the anti-leukemia activity of the two agent combination as assessed by overall response (CR, CRi) rate, in patients with relapsed/refractory ALL. The study is expected to enroll and treat a minimum of 12 and a maximum of 30 patients at the recommended phase 2 schedule. The sample size is based on the desire to discriminate a promising CR/CRi rate of 64% from a disappointing response rate of 44% [15] using a type I error rate of 0.10 and power of 80%. At stage 1, 12 patients will be entered on the study. If ≤ 5 complete remissions are seen, the study will be terminated. If at least 6 patients achieve CR/CRi, the trial will continue to the second stage. At stage 2, 18 additional patients will be entered. At the end of stage 2, if 17 or more patients experience complete remission, the combination will be considered worthy of further study. If ≤ 16 patients experience a complete remission then no further investigation of the combination is warranted.

5.2 **Treatment**

The pembrolizumab (200mg) and blinatumomab doses (28 µg/day) are fixed except that blinatumomab is given at 9 µg/day on days 1 to 7 during cycle 1. If safe and tolerable, patients who do not progress may receive up to 5 cycles of combination treatment. For cycles 2 and beyond, pembrolizumab should be administered first, with blinatumomab given at least an hour after the completion of the pembrolizumab infusion. Patients who achieve CR at any time may opt to go on to alloHSCT. Patients who have completed 5 cycles of combination therapy or are intolerant to pembrolizumab after cycle 1 may continue receiving single-agent blinatumomab, for a total of up to nine (9) cycles of blinatumomab, according to the schedule in the prescribing information.

5.3 **Definition of Dose Limiting Toxicity (DLT)**

All toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.

During the phase 1 portion, the occurrence of any of the following toxicities will be considered a DLT if judged by the Investigator to be possibly, probably, or definitely related to the administration of either immunotherapy agent in the treatment regimen and occur during cycle 1. DLTs are defined as follows:

- Grade 4 or above non-hematologic toxicity with the exception of nausea and vomiting (if manageable with supportive care measures), alopecia, and toxicities secondary to neutropenia and sepsis
- Grade 4 neutropenia lasting ≥42 days from the start of therapy in the absence of evidence of active leukemia
- Hypocellular marrow (<5%) without evidence of leukemia that lasts more than 42 days from the start of therapy
- Any grade 3 non-hematologic toxicity with the exception of alopecia, or toxicities secondary to neutropenia and sepsis that do not resolve to grade 2 or better or baseline by 7 days.
- Treatment delay in start of cycle 2 of more than 2 weeks due to toxicity associated with the study treatment.
- Inability to administer most of the planned doses for both drugs during cycle 1:
    - missed pembrolizumab dose due to toxicity associated with the study treatment will be considered as a DLT
    - Seven or more consecutive days of missed blinatumomab treatment due to toxicity associated with the study treatment will be considered as a DLT

The following events will not be considered DLTs

- Grade 3 or 4 tumor lysis syndrome
- Any AEs related to malignancy or pre-existing conditions

Note: These same criteria will be used to define unacceptable toxicity during the phase 2 portion of the trial.

5.4 Blinatumomab Dosing and Supportive Care

Blinatumomab must be administered using infusion pumps approved for use by the appropriate regulatory authorities for the country in which the subject is undergoing treatment, in both the inpatient and outpatient setting.

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 (except for Schedule A Cycle 1, with a 1-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 cycle, the initial dose of blinatumomab will be 7 days of 9 μg/day by continuous infusion, which then will be increased (dose step) to 28 μg/day continuous infusion, starting on day 8 (week 2) through day 29 (week 4). For all subsequent cycles 28 μg/day will be the dose for 4 weeks of continuous treatment.

The drug administration should not be interrupted. 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 in the hospital, under the supervision of the investigator. The subject should be observed over night for possible side effects after the re-start, either in the hospital or in the outpatient setting as applicable. Administration of the 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.

The daily blinatumomab dose may be up to 10% lower or higher in order to account for possible pump inaccuracies.

A dose of up to 10% higher than the intended dose may not require specific intervention. In case of overdose or medication error, the infusion should be immediately stopped. Routine supportive and symptomatic care according to standard medical practice is recommended. Once the subject is stable and no clinically relevant safety findings due to blinatumomab are observed, resumption of blinatumomab at a correct dose can be considered after consultation with the medical monitor.

If the overdose results in an adverse event, the subject should be followed carefully until all signs of toxicity are resolved and the adverse event/s is to be recorded/reported per protocol.

The dose, start and stop date/time is to be recorded on each subject's CRF.

5.4.1 Blinatumomab Inpatient Dosing

It is required that subjects are hospitalized at least during the first 9 days, as well as days 15 and 16 of the first cycle. Additional hospitalization time depends on investigator´s judgment, as well as the safety and tolerability of blinatumomab combined with pembrolizumab.

The infusion bags will be changed by site nursing personnel. Close monitoring during the first 48 hours of treatment in the first 2 cycles will be indicated because of the potential AEs associated with T-cell redistribution and potential cytokine release effects triggered by the administration of blinatumomab. Nurses/physicians trained in emergency medicine should be available for immediate intervention in case of complications. Subsequent treatment administration may be continued on an outpatient basis, if it is judged to be safe and feasible by the investigator

5.4.2 Blinatumomab Outpatient Dosing

In the outpatient setting, the subject will typically return to the study site for changes of infusion bags at intervals of 5-7 days as specified in the study calendar to change the infusion bag, coinciding with scheduled weekly visits. However, if it is not possible to coordinate the bag change with a scheduled visit, it is acceptable to allow home health or a local infusion clinic per SOC to perform the bag change, as long as the patient is assessed weekly in clinic. In addition, the subject will visit the study site for the examinations according to Schedule of Assessments.

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.

In case of any adverse event in the outpatient setting, the subject and/or his/her legal representative or, if applicable, the ambulant/home care or infusion clinic provider should directly contact the investigator at the study center for further management.

5.4.3 Blinatumomab Supportive Care

5.4.3.1 Dexamethasone Premedication

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment.

Table 3 below summarizes dexamethasone use prior to blinatumomab treatment during different phases of the study.

Table 3. Dexamethasone Premedication

Treatment Phase	Target Patient	Dexamethasone Dose
Pre-phase Therapy Before Blinatumomab	During Screening and Prior to start of treatment:	Dexamethasone 10mg/m²/day can be administered up to 5 days during screening and until 3 days prior to

	Mandatory for: Proportion of Blasts exceeds approximately 50%, or Peripheral blast count ≥15,000/µL Recommended for: LDH indicates rapidly progressing disease, or extramedullary high tumor load	initiation of blinatumomab. If indicated dexamethasone dose can be increased to an absolute maximum of 24 mg/day
Pre-dose Dexamethasone Prior to Each Blinatumomab Treatment	All patients (before each cycle and dose step/increase)	Dexamethasone 20 mg IV: within 1 hour prior to start of treatment in each treatment cycle, and within 1 hour prior to dose step (increase).
Infusion Interruption/Dose Modification Due to Adverse Event	Patients who interrupt treatment > 4 hours	Dexamethasone 20 mg IV: within 1 hour prior to re-start of treatment
In case of signs of cytokine release	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.

5.4.3.2 Pre-phase Therapy before Blinatumomab Treatment

Premedication with dexamethasone is intended to prevent CRS events associated with blinatumomab treatment. Please refer to Table 3 for pre-phase dosing instructions with dexamethasone

For this study, mandatory pre-phase therapy with dexamethasone is required prior to blinatumomab treatment if one or more of the following criteria are met:

- Proportion of blasts (determined by cytomorphology) exceeds approximately 50% or
- peripheral blood blast count ≥15,000/µL

Pre-phase therapy with dexamethasone is recommended prior to blinatumomab treatment if, in the opinion of the investigator:

- LDH indicates rapidly progressing disease, or
- signs of extramedullary disease show high tumor load.

Pre-phase dexamethasone at a dose of 10 mg/m^2/day can be administered up to 5 days during the screening and until 3 days prior to the planned initiation of blinatumomab. If clinically indicated, the dexamethasone dose can be increased to an absolute maximum dose of 24 mg/day.

If the subject received dexamethasone (up to 24 mg/day) for other reasons than pre-phase within 14 days prior to start of screening, further pre-phase treatment with dexamethasone is not required. However, premedication with dexamethasone is required within 1 hour prior to start of treatment in each treatment cycle and within 1 hour prior to the dose step as described in Table 3.

It should be noted that in cases of ALL that are refractory to dexamethasone treatment, a preventative effect on CRS can still be achieved. If a subject is refractory to dexamethasone, a pre-phase is not mandatory, but

dexamethasone at a dose of at least 24 mg/day should be administered at least for the first 2 days of treatment with step-wise reduction afterwards.

Subjects who should receive dexamethasone treatments of at least 24 mg/day and who have already received the mandatory 20 mg IV premedication dose prior to blinatumomab infusion at day 1, may receive the remaining daily doses of dexamethasone as follows: at least 2 x 2 mg schedule on day 1 and at least 3 x 8 mg on day 2.

5.4.3.3 Pre-dose Dexamethasone Prior to Each Blinatumomab Treatment

Within 1 hour prior to start of treatment in each treatment cycle and within 1 hour prior to dose step, mandatory premedication with dexamethasone at 20 mg IV is required for the prevention of CRS resulting from blinatumomab.

5.4.4 CNS Prophylaxis before Blinatumomab Treatment

Within 1 week (±3 days) prior to start of blinatumomab for each treatment cycle, a mandatory CSF prophylaxis consisting of an intrathecal regimen according to institutional or national guidelines will be administered (e.g., methotrexate 12 to 15 mg, cytosine arabinoside 40 mg, and dexamethasone 4mg or equivalent steroid dose).

5.5 Pembrolizumab Dosing and Supportive Care

5.5.1 Timing of Dose Administration

Pembrolizumab should be administered on the prescribed day, depending on cycle and cohort, after all procedures/assessments have been completed as detailed in the Study Evaluations table (Section 10.0).

Pembrolizumab will be administered at a flat dose of 200 mg as a 30-minute IV infusion every 3 weeks. A window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Pembrolizumab may be infused through a central line used for continuous blinatumomab infusion if it is through a separate lumen to ensure no mixing of medication at any time.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.5.2 Pembrolizumab Supportive Care and Rescue Medications

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below in **Table 4** for infusion related reactions and in **Section 6.2, Table 5** for drug-related toxicities and severe or life-threatening immune-related adverse events (irAEs). Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

5.5.2.1 Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Table 4** below.

Table 4. Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g.,	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine* IV fluids Antihistamines NSAIDS Acetaminophen	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. *In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

5.6 **Concomitant Therapy**

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the section below.

5.6.1 Excluded Treatments during the Study Period

The following medications are not permitted during a subject's participation during treatment phase (including the induction, consolidation phases of treatment) of this study:

- Any anti-tumor therapy other than the blinatumomab and pembrolizumab:
  - Cytotoxic and/or cytostatic drugs. IT chemotherapy is allowed for CNS prophylaxis per treating physician recommendation in between cycles throughout the study.
  - Radiation therapy
- Chronic systemic (> 7 days) high-dose corticosteroid therapy (dexamethasone > 24 mg/day or equivalent)
  Any other immunosuppressive therapies (except for transient use of corticosteroids)

5.6.2 Additional Risks in Marrow or Organ Transplant Recipients

Subsequent allogeneic HSCT: Patients undergoing alloHSCT following treatment with pembrolizumab have an increased risk of post-transplant complications including severe GVHD and veno-occlusive disease (VOD).

Previous allogeneic HSCT: Patients who have previously undergone alloHSCT may develop severe GVHD following pembrolizumab therapy.

Previous organ transplant: Patients who have previously undergone organ transplant may experience rejection of the transplanted organ following pembrolizumab therapy.

5.6.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.6.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs (as defined in Section 7.5.2.)

5.6.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Immunotherapy not specified in this protocol, excepting tocilizumab for management of CRS.
- Chemotherapy not specified in this protocol
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Corticosteroids or any other immunosuppressive therapies are not allowed throughout the study excepting dexamethasone premedication for blinatumomab, for management of CRS and neurologic toxicities, or physiologic replacement prednisone or equivalent ≤ 10 mg/day.
- GMCSF within 2 weeks of study treatment and throughout the study is not allowed.
- Use of GCSF is not recommended during the first 14 days of study treatment. Its use for the remaining study period is based on treating physician's discretion.
- Live vaccines or live-attenuated vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Administration of killed vaccines is allowed. Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

5.7 **Contraception**

Pembrolizumab and blinatumomab may have adverse effects on a fetus in utero. Furthermore, it is not known if whether these study agents have transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of pembrolizumab and 48 hours after the last dose of blinatumomab.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period (120 days after last pembrolizumab dose and 48 hours after the last dose of blinatumomab for both women and men). If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.8 **General Supportive Care**

5.8.1 Hydration during the Treatment Period

Because of the high tumor load, subjects should receive adequate hydration according to institutional guidelines.

The schedule of hydration and management of urine alkalization should be determined by monitoring the clinical condition, the urine pH, creatinine, urea/BUN, as applicable, uric acid, and LDH. The subject should be weighed, and diuretic drugs should be administered accordingly. These measures should be applied as long as considered necessary by the investigator.

5.8.2 Fever Management

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided if possible because they are a potential cause of endothelial stress and could potentially affect T-cells that are required for blinatumomab action. For symptomatic relief of fevers due to any cause (i.e. infection, drug fever) the recommended first choice for fever management are paracetamol/acetaminophen and/or dexamethasone. The dexamethasone dose should be reduced step-wise as soon as the fever is resolved. If these are not sufficiently effective, pethidin/meperidine is recommended. For pethidin/meperidine, adequate antiemetic prophylaxis should be administered. The treating physician should also use their clinical judgement to determine the underlying cause of the fever and treatment. For instance, in the case of fever due to infection one should consider the use of antibiotics and avoid the use of dexamethasone.

5.9 **Withdrawal of Subjects**

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. The COH DCC should be promptly notified of the change in participant status.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-specified therapies or procedures at any time during the study but continue participation in the study. If this occurs, the Investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-specified therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 7) and collection of data, including endpoints and adverse events. The Investigator must document the change to the Schedule of Assessments (Table 7) and the level of follow-up that is agreed to by the subject (e.g., in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-specified therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The Investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

Reasons for removal from protocol-required investigational product(s) are:

- investigator decision that a change of therapy (e.g., immediate alloHSCT) is in the subject's best interest
- subject request
- safety concern (e.g., due to toxicity of investigational product(s) or other an adverse event)
- decision by sponsor
- death
- lost to follow-up
- disease progression

Reasons for removal of a subject from the study might include:

- withdrawal of consent from study
- death
- lost to follow-up

Subjects who withdraw prior to receiving protocol-directed therapy will be replaced. During the phase 1 portion: patients considered inevaluable for dose-escalation will be replaced. During the phase 2 portion: patients considered inevaluable for response will be replaced.

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment (EOT) assessments, and then to follow-up (**Section 5.10** below).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of any change in participant status.

5.10 **Follow-Up**

5.10.1 Safety Follow-up Visit

All subjects, including subjects who withdraw early, should complete a safety follow-up (SFU) visit 30 days (± 7 days) after the last dose of study drug, or prior to further alloHSCT/chemotherapy, if applicable.

Assessment time points and windows are detailed in **Section 10.0**.

The COH DCC and the Study PI should be promptly notified of any change in participant follow-up status.

5.10.2 One Year Follow-up ± SOC alloHSCT or Single-agent Blinatumomab

All subjects will be followed in the long-term follow-up (LTFU) portion of the study for safety, duration of disease remission and overall survival, as well as limited toxicity assessments, depending on the type of additional treatment after completion of the prescribed therapy.

5.10.2.1In CR, with subsequent allogeneic transplantation (SOC)

For patients who go on to allogeneic transplantation after completion of prescribed study therapy, transplant data from CIBMTR forms/COH transplant registry will be utilized:

- Disease status (using SOC biopsy results post-alloHSCT)
- Date of transplant
- Conditioning regimen
- GVHD prophylactic regimen
- Time to neutrophil and platelet engraftment
- Acute GVHD max grade and date of onset
- Chronic GVHD max grade and date of onset
- Date of relapse
- Date of death
- Cause of death
- Last contact date

5.10.2.2In CR, transplant ineligible (or declining) receiving single-agent blinatumomab SOC

Participants in CR who have completed 5 cycles of therapy or have discontinued pembrolizumab after cycle 1 due to intolerability, may opt to continue receiving blinatumomab on this protocol for a total of 9 cycles per SOC. Blinatumomab 28 μg will be administered CIV per schedule in the prescribing information. Physical, vitals, lab tests will be performed at clinic visit prior to the first day of each blinatumomab dosing cycle per SOC. In addition, participants will be followed via clinic or telephone contact every 3 months (± 2 weeks) after their safety follow-up (SFU; see Section 10 Study Calendar) visit to assess disease status for 1 year after start of therapy, or until death, whichever occurs first. Information related to subjects' health condition including duration of response, toxicity (only grade 3/4) and overall survival may be obtained. The following procedures will be completed at least every 3 months (± 2 weeks):

- Hematology with chemistries and differential
- Bone marrow aspirate/biopsy (morphological assessment only) every 3 months
- Documentation of concomitant medications limited to start/stop date and indication
- Grade 3/4 toxicities recorded and followed until resolution to grade 1/2 or baseline
- Disease/Survival status

5.10.2.3In CR with no further therapy (blinatumomab not tolerated or declined / transplant ineligible or declined)

Subjects in CR who receive no further treatment after completing 5 cycles of therapy will be followed via clinic or telephone contact every 3 months (± 2 weeks) after their safety follow-up visit to assess disease status for 1 year after start of therapy, or until death, whichever occurs first. Information related to subjects' health condition including duration of response, toxicity (only grade 3/4) and overall survival may be obtained.

The following procedures will be completed:

- Bone marrow aspirate/biopsy (morphological assessment only)
  -Every effort should be made to perform BM aspirate/biopsy until relapse is confirmed

- Hematology with chemistries differential
- Documentation of concomitant medications limited to anti-leukemic treatments
- Disease/Survival status
- Grade 3/4 toxicities recorded and followed until resolution to grade 1/2

5.10.2.4Relapse/progression

Patients who have documented progression on study therapy will continue to be followed for survival only for up to 1 year after start of therapy.

5.10.3 Survival Follow-Up

Survival information only will be collected from patients for the duration of the study, i.e. until the last patient treated has completed their 1 year follow-up.

6 Dose Delay/Modifications (Treatment Interruptions, Holds, Criteria for Restarting Treatment)

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

6.1 **Blinatumomab**

6.1.1 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 infection, cytokine release syndrome, tumor lysis syndrome, and 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 the adverse event 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 adverse event has resolved to grade 1 or less for at least 7 days.

Re-start of the infusion should be performed in the hospital, under supervision of the investigator. Before blinatumomab is re-started, premedication with dexamethasone must be administered as described in **Table 3**. The subject 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 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 dose.

If the interruption after AE 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 AE 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 not be counted as an evaluable cycle for the primary endpoint and will have to be repeated (e.g., 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 AE 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 AE 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 up to 3 days. The dose should then be reduced step-wise over 4 days.

6.1.2 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 AEs, blinatumomab will be stopped immediately and a physical exam, vital signs and safety laboratories will be performed. Additional measures can be taken upon discretion of the investigator, depending on the nature of the AE. 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 an Amgen medical monitor. 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, under supervision of the investigator 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. There will be no dose escalation on day 8 or for the following cycles. The recommendation for treatment modification in case of CNS events is based on the experience gained in the phase 2 studies MT103-206 and MT103-211. After restarting blinatumomab vital sign measurements, the Mini-Mental Status Exam (MMSE) and writing tests (See **Appendix 18.3** for writing test and **Appendix 18.4** for MMSE form) should be performed for the next 3 days.

If the CNS event was a seizure (CTCAE grade 2 or above), appropriate prophylactic anticonvulsant treatment (a therapeutic dose of e.g., phenytoin or levetiracetam) 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 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. The investigations associated with and previously described for a CTCAE grade 3 or higher CNS-related AEs, must also be performed.

An MRI is recommended for subjects who permanently discontinue treatment because of a CNS event ≥ grade 3.

6.1.3 Criteria for Discontinuation of Blinatumomab

Treatment with blinatumomab should be discontinued in the event of any of the following:

- Hematological or extramedullary relapse subsequent to CR/CRi on protocol treatment
- 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.
- Occurrence of an AE which makes discontinuation from treatment necessary due to protocol specified safety criteria or desirable in the investigator's and/or the subject´s opinion
- An infusion interruption of more than 2 weeks due to an AE 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)
- Occurrence of CNS-related adverse event meeting one or more of the following criteria:

  -More than one seizure

  -A CNS-related adverse event CTCAE grade 4

  -A CNS-related adverse event leading to treatment interruption that needed more than 1 week to resolve to CTCAE grade ≤ 1

  -A grade 3 CNS-related adverse event leading to treatment interruption that occurred at a dose of 9 µg/day

  For subjects who discontinue treatment because of a CNS event ≥ grade 3, an MRI is recommended.

- Investigator's decision that a change of therapy (including immediate alloHSCT) is in the subject´s best interest
- Administration of relevant non-permitted concomitant medications
- Investigator's decision that a subject does not benefit from treatment anymore (e.g., non-response or development of progressive disease)
- Intercurrent medical condition, which in the opinion of the investigator or the subject precludes further treatment of the subject
- Withdrawal of subject's consent to study treatment

All reasons for treatment discontinuation will be documented in the CRFs. If a subject fails to keep the appointments for study visits, the investigator will document the reason and circumstances as completely and accurately as possible.

In case of premature treatment discontinuation, the assessments planned for day 29 (end of infusion) should be performed immediately. Exceptions: The CSF examination/prophylaxis does not have to be done in case of premature treatment discontinuation. Bone marrow aspiration/biopsy is not required in case of documented progressive disease. In addition, the safety follow-up visit should be performed 30 days after the last dose of blinatumomab was administered or, if applicable, prior to the start of non-blinatumomab or

alloHSCT, whichever occurs first. The subject should continue to come to all relevant long-term follow-up visits.

6.2 Pembrolizumab Dose Modification/Discontinuation and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab and Immuno-Oncology (IO) Partners (Blinatumomab)

There will be no modification of the dosage of pembrolizumab in this trial; however, the drug may be withheld or discontinued. Adverse events (both non-serious and serious) associated with pembrolizumab or blinatumomab or combination exposure, may represent an immunologic etiology. These immune-related adverse events (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening irAEs as per **Table 5** below (next page).

For management of infusion-related reactions, refer to **Table 4 in Section 5.5.2.1.**

For any other non-infusion related and non-immune treatment-related adverse reactions grade 3 or greater, withhold pembrolizumab until adverse reactions recover to Grade ≤1.

Attribution of Immune-Related Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to blinatumomab alone or to pembrolizumab alone, for adverse events listed in **Table 5**, both interventions must be held according to the criteria in **Table 5**.

Note: If continuing with blinatumomab is considered to be in the patient's best interest and the adverse event is thought to be most likely to be attributable to the pembrolizumab, then the blinatumomab may be continued at the discretion of the investigator.

Note: The AE data collection includes attribution assignment by agent, not combination.

Holding Study IO Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both IO interventions (pembrolizumab and blinatumomab) should be held according to recommended dose modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must discontinue all IO therapy (both pembrolizumab and blinatumomab).

Note: If continuing with blinatumomab is considered to be in the patient's best interest and the adverse event is thought to be most likely to be attributable to the pembrolizumab, then the blinatumomab may be continued at the discretion of the investigator.

Restarting Study Interventions:

Participants may restart pembrolizumab and blinatumomab, as described below.

- If the toxicities do resolve and conditions are aligned with what is defined in **Table 5**, the combination of blinatumomab and pembrolizumab may be restarted at the discretion of the investigator.

Table 5. Dose modification and toxicity management guidelines for immune-related AEs (irAEs) associated with pembrolizumab and IO combination partner (blinatumomab)

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. All IO treatments (pembrolizumab and blinatumomab) must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.

Note: If continuing with blinatumomab is considered to be in the patient's best interest and the adverse event is thought to be most likely to be attributable to the pembrolizumab, then the blinatumomab may be continued at the discretion of the investigator.

3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If IO treatments have been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade or conditions (CTCAE v5.0)	Action With Pembrolizumab + Blinatumomab[f]	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity grade or conditions (CTCAE v5.0)	Action With Pembrolizumab + Blinatumomab[f]	Corticosteroid and/or other therapies	Monitoring and follow-up
				feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2	Continue		

irAEs	Toxicity grade or conditions (CTCAE v5.0)	Action With Pembrolizumab + Blinatumomab[f]	Corticosteroid and/or other therapies	Monitoring and follow-up
	Grade 3 or 4	Withhold until clinically stable or permanently discontinue [d]	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grades 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
	Persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes

irAEs	Toxicity grade or conditions (CTCAE v5.0)	Action With Pembrolizumab + Blinatumomab[f]	Corticosteroid and/or other therapies	Monitoring and follow-up
All other immune-related AEs	Grade 3	Withhold or discontinue based on the event. [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab or its IO combination partner is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab or its IO combination partner may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

f If continuing with blinatumomab is considered to be in the patient's best interest and the adverse event is thought to be most likely to be attributable to the pembrolizumab, then the blinatumomab may be continued at the discretion of the investigator.

7 Reporting of Adverse Events, Unanticipated Problems & Other Events of Interest

7.1 Adverse events and Unanticipated Problems

The research team is responsible for classifying AEs and UPs as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

7.2 Assessment of Adverse Events

The Study PI will be responsible for determining the event name, assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in the most recent version of the NCI CTCAE v5.0. A copy of the scale can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.
The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

7.2.1 Adverse Events of Special Interest (AEOSI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events, regardless of seriousness, will be reported as indicated to Merck or Amgen. This will include overdose of either blinatumomab or pembrolizumab, as well as events of clinical interest for pembrolizumab.

7.2.1.1 Events of Clinical Interest (ECI) for pembrolizumab

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.1.4.2.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow- up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.1.2 Definition of a Pembrolizumab Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For the purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.1.3 Definition of a Blinatumomab Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Amgen

For purposes of this trial, an overdose of blinatumomab will be defined as any dose ≥ 10% more than the planned dose. No specific information is available on the treatment of overdose of blinatumomab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of blinatumomab, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

7.3 Routine AE Collection and Reporting Guidelines

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until end of study participation, which may be up to 1 year following start of treatment. Adverse events will be monitored by the Protocol Management Team (PMT). AEs that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

7.3.1 AE Data Collection in the DLT Period

Toxicity collection during the first cycle will be the purpose of determining DLT. During Cycle 1, only the worst grade of each toxicity will be collected, with the exception of toxicities secondary to neutropenia or sepsis. For these exceptions all grade changes, including start and stop dates for each, will also be captured.

7.3.2 AE Data Collection in Cycles 2+

Toxicity collection after the DLT period, for patients in CR who continue to undergo the prescribed cycles of treatment (until the SFU visit) will include only the worst of grade 3/ 4 toxicities, which will be followed until documentation of resolution to grade 1 or 2. Documentation of concomitant medications during treatment will be limited to start/stop date and indication.

7.3.3 Long-Term AE Monitoring/Data Collection

Toxicity collection during the long-term follow-up period depends on disease status and subsequent therapy and is described in **Section 5.10.2**.

Participants who withdraw from the study will be followed for adverse events for 30 days following last dose of study drug, or until resolution of grade 3/4 adverse events, whichever is longer.

7.4 Expedited Reporting

Table 7.4 indicates what events must be reported expeditiously.

Table 7.4 Criteria for Expedited Reporting

Time point	What to report
From signing of the consent to study completion	All UPs
For the time period beginning at treatment through 30 days following cessation of treatment	All SAEs regardless of relationship to protocol therapy All UPs and AEs that meet the definition of a UP
From day 1 of protocol therapy up to 120 days post-last pembrolizumab and 48 hours post-last dose blinatumomab or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier	Pregnancies and lactation
Post Safety Follow-Up to removal from study	All SAEs that are considered possibly, probably or definitely related to pembrolizumab or blinatumomab
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator.	

The DCC should be consulted prior to ending the follow-up of events that have stabilized.

7.4.1 Expedited reporting guidelines **(COH only)**

7.4.1.1 To the COH DSMC/IRB

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites. For non-COH sites, the DCC will be responsible for reporting (see **Section 7.4.2**).

7.4.1.2 To Participating Investigators

Report all expedited reportable AEs to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (COH) notification and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed (if applicable), and, for non-COH sites, a statement that the report should be submitted to their local IRB for review if applicable per local IRB policy.

Forward to participating sites all external IND safety reports received from Amgen or Merck, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

7.4.2 Expedited reporting guidelines **(non-COH sites only)**

7.4.2.1 To the DCC/Study PI

All events that meet the criteria specified in **Table 7.4** will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the AE/UP on each of the following:
   a. MedWatch 3500A or local IRB submission document*
   MedWatch 3500A is downloadable form at http://www.fda.gov/medwatch/getforms.htm
   *The local IRB submission document may be used if the document template is approved by the DCC
   b. Expedited Reporting Coversheet. A modifiable Microsoft Word document is available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the Study PI (ebudde@coh.org) and DCC@coh.org with the subject title as "Blina/Pembro for B-cell ALL SAE COH IRB #19017".

   If available, sites may include the local IRB submission for this event in the submission.
4. If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

7.5 **Reporting to the FDA**

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, regardless of the site of occurrence, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

The final IND report will be distributed to the Study PI and DCC. If it is determined that the IND safety report requires a change to the protocol or the consent form, the DCC will include instructions to participating sites for local IRB reporting.

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

7.6 Reporting to Merck

Any serious adverse event (SAE), or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 business days but no longer than 3 calendar days to Merck Global Safety. Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs. Additionally, any SAE, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.
All subjects with serious adverse events must be followed up for the outcome.

7.7 Reporting to Amgen

All suspected unexpected serious adverse reactions (SUSARs) related or possibly related to blinatumomab and their follow-up reports must be reported to Amgen within 24 hours of submission to the regulatory agency, IRB or IEC. A copy of any safety report involving an Amgen drug (e.g. blinatumomab) submitted to the regulatory agency, IRB or IEC, must be faxed to Amgen, within 24 hours of such submission at **FAX Toll-free #:1-888-814-8653 Attn: Amgen Global Safety**. In addition, there will be a 6-monthly SAE line listing submitted to Amgen Global Safety.

7.8 Pregnancy and Lactation Reporting

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. **Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI and the DCC immediately within 24 hours of awareness**. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy, and should notify the Study PI.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines.

Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines. The Study PI or designee will subsequently inform Merck (pembrolizumab) and Amgen (blinatumomab) (**Section 7.6 and 7.7**).

7.8.1.1 Pregnancy

If a subject inadvertently becomes pregnant while on study, the subject will immediately be removed from the study. The Sponsor must report all pregnancies and pregnancies occurring in the partner of a patient participating in the study within 2 business days but no longer than 3 calendar days of sponsor's awareness to Amgen and Merck. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the City of Hope DSMC / IRB and to Merck and Amgen without delay. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

7.8.1.2 Use in Nursing Women

It is unknown whether pembrolizumab or blinatumomab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. The Sponsor must report any potential infant exposure through lactation within 2 business days but no longer than 3 calendar days of sponsor's awareness to Merck and Amgen.

8 Investigative Agent Information

8.1 **Blinatumomab**

Blinatumomab will be manufactured and packaged by Amgen Inc. The term "pre-phase therapies" used throughout the protocol refers to other protocol-mandated medication (e.g., pre-phase with dexamethasone or intrathecal prophylaxis).

8.1.1 Formulation, packaging, and storage

Blinatumomab will be supplied as 3-mL single-use glass injection vials containing a sterile, preservative-free, white to off-white, lyophilized powder for intravenous (IV) administration following reconstitution with sterile water for injection (sWFI). Each vial contains 35µg blinatumomab formulated with 25mM citric acid monohydrate 15% (W/V) trehalose dihydrate, 200 mM lysine hydrochloride, and 0.1% (W/V) polysorbate 80, pH 7.

Since blinatumomab will be administered via continuous intravenous route, it needs to be stabilized at low concentrations to prevent absorption to surfaces. Therefore, the normal saline 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.

8.2 **Pembrolizumab (MK-3475; KEYTRUDA®)**

8.2.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Pembrolizumab will be provided by Merck as:

- Pembrolizumab 100 mg/ 4mL Solution for Injection

8.2.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

8.2.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.2.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.2.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9 Correlative Studies

9.1 Biological Sample Collection for Biomarker Studies

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response including efficacy and/or adverse events. Samples (**Table 9.1**) will be tracked using a unique identifier that is assigned to each sample for the study. Results are stored in a secure database to ensure confidentiality.

Table 9.1: Research sample collection

Specimen	Tube	# of tubes	Volume (mL)/tube	Total Volume	Deliver to	Purpose
Bone Marrow Aspirate[1]	Lavender EDTA (6 mL)	2	4 - 5 mL	10 mL	HTB Kaplan 2007[1, 2]	Research/Budde Lab/ClonoSeq[3]
	Slides from bone marrow core biopsy block	1 H&E 5 blank	NA	NA	Pathology[1]	Research/Budde Lab/IHC
Whole Blood	Red serum (6 mL)	1	4 - 5 mL	5 mL	HTB Kaplan 2007[1, 2]	Research/Budde Lab
	Lavender EDTA (6 mL)	5	4 - 5 mL	30 mL	HTB Kaplan 2007[1, 2]	Research/Budde Lab
Stool	Zymo Research DNA/RNA Shield fecal storage tube (brown cap)	1	1 mL	1 mL	HTB Kaplan 2007[1, 2]	Research/TGen/ microbiome
	Sterile SARSTEDT feces tubes (76 x 20 mm) with standard label (brown cap) (inpatient only)[4]	2	1 mL	2 mL	HTB Kaplan 2007[1, 2, 4]	Research/TGen/ microbiome

1. Research BMA, blood, stool and core biopsy slides from screening/staging visit will be obtained from Pathology only after participant study enrollment. Contact Pathology for sample scheduling and notification.
2. Please include Tinisha McDonald (tmcdonald@coh.org) and Lucy Ghoda (lghoda@coh.org) of the Hematopoietic Tissue Biorepository (HTB) on the CRC email for sample scheduling and notification.
3. CRC to update study team within 1 week prior that a ClonoSeq BMA sample will be shipped.
4. Inpatient feces samples should be put on dry ice (or in a freezer if it's collected after work hours) within 30 min of collection prior to pickup by the HTB who will deidentify and freeze -80°C immediately.

Note: The order of tube collection should be per Clinical and Laboratory Standards Institute (ex. Order of draw: sodium citrate tube, serum tube, heparin tube, EDTA tube). It is acceptable to use other available tube sizes to ensure collection of the required volume of blood.

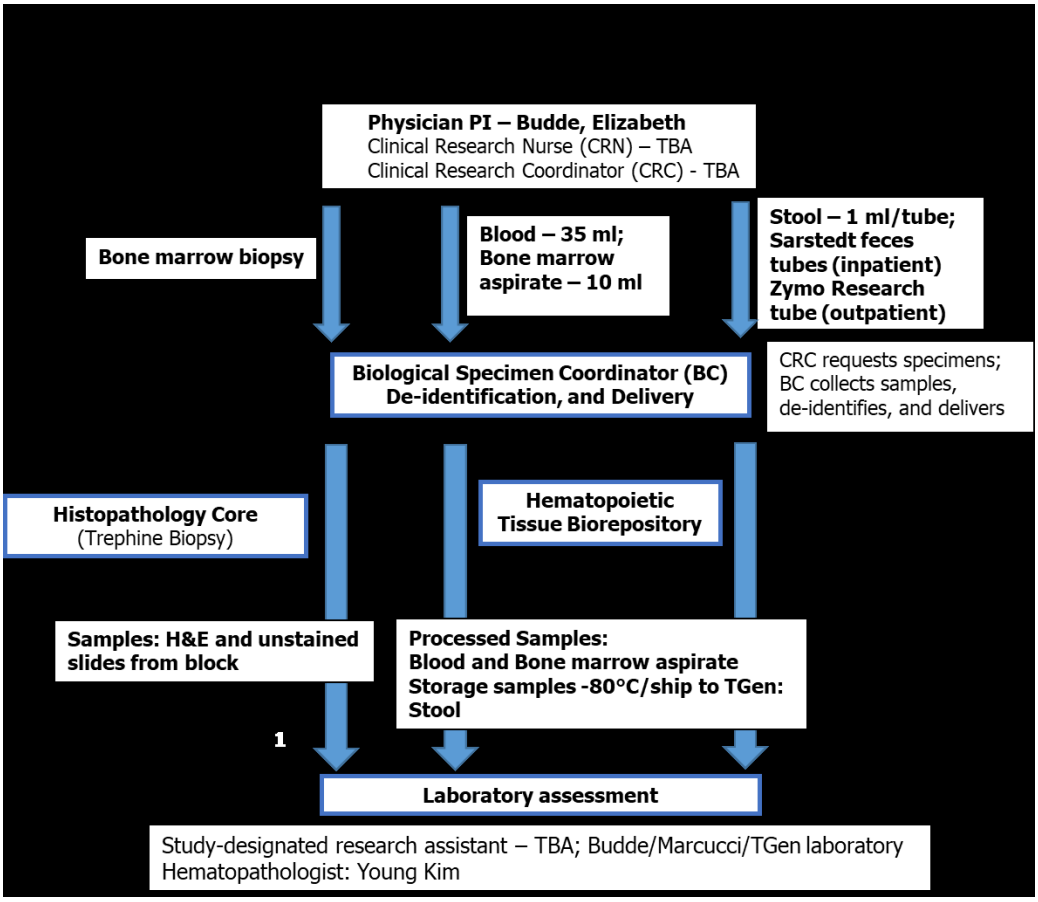
All correlative samples will be analyzed at the Budde or Marcucci labs at COH or at Translational Genomic Research Institute (TGen; Phoenix, AZ) in batches.

Liquid samples (blood and bone marrow aspirate) and stool samples will be shipped to/stored at the Hematopoietic Tissue Biorepository (HTB) prior to disbursing/shipping to the labs.

A **Correlative Tissue Form** is to accompany samples (**Appendix 18.5**).

For **Tissue Shipping Guidelines to City of Hope HTB** see **Appendix 18.7**.

Below is a flow chart detailing the biological samples collection, personnel and locations involved at City of Hope. Up to 10 mL bone marrow aspirate will be collected and up to 35 mL blood will be collected at time points designated in the study calendar,



- **Peripheral blood (PB)** will be collected for biomarker correlative studies pretreatment. One 35 ml blood draw (in one x 6 ml red top serum tube and five x 6 ml lavender top EDTA tubes) is to be collected weekly at cycle 1 day 1 prior to blinatumomab dose on days 8, 15, 22, 29, day 36 ± 1 days (only for Schedule B) and at the end of each subsequent cycle (day 36 ± 1 days). Blood samples will be placed at room temperature for pickup by the HTB within 1 hour of collection, processed to cells and plasma (and serum for the red top serum tube) by the HTB per their SOPs, stored and dispensed to Dr. Budde's lab.
- **Bone marrow (BM)** will be biopsied/aspirated pre-treatment and at the end of each cycle, 3-7 days prior to start of cycle 2 and 1-14 days before start of subsequent cycles until CR is

documented (first of 2 consecutive leukemia-free biopsies). Bone marrow aspirate (BMA) will be collected in two x 6 ml lavender top EDTA tubes (10ml total). The HTB will process the BMA cells and provide Dr. Budde's lab with the stored cells and plasma. One BMA sample will be sent for ClonoSeq. One H&E and 5 blank slides from the bone marrow core biopsy block will be collected. After CR is attained, biopsies for patients remaining on treatment will be every other cycle until the end of treatment and every 3 months thereafter (unless patient has relapsed, proceeded to allogeneic transplantation, or withdrawn from study). Additional bone marrow biopsy samples will be collected for research biomarker assays at the safety follow-up (SFU) visit, if the subject ended treatment for any reason other than relapse.

- **Stool Samples (inpatient)** will be collected in one Zymo Research DNA/RNA Shield fecal storage tube (brown cap; 1 mL stool/tube) and two sterile SARSTEDT feces tubes (76 x 20 mm) with standard label (brown cap; 1 mL stool/tube), with the schedule specified in the study calendar (**Section 10**). Stool samples will be collected according to standard operating procedures modified from the NIH Human Microbiome Project protocols. Briefly, collected stool samples (collected in Zymo Research DNA/RNA Shield fecal storage **Appendix 18.6** and SARSTEDT feces tubes) will be placed on dry ice within 30 minutes of collection and for no more than 72 hours prior to freezing at -80°C storage at the HTB. De-identified, frozen stool samples will be stored at the HTB until shipment to TGen.
- **Stool samples (outpatient; Section 10)** will be collected at screening within one week of initiation of study treatment. Another stool sample will be subsequently collected before the first pembrolizumab treatment and at the end of cycles 1 and 2. Outpatient participants will be sent home with an "at home stool sample collection kit" consisting of a Zymo Research DNA/RNA Shield fecal storage tube and instructions on how to collect samples (**Appendix 18.6**). Participants should be advised to FedEx or bring the sample back to the medical center on their next visit (if within one week). FedEx shipping label should be provided with the at home sample collection kit.

9.2 Biomarker Analysis

9.2.1 Composition of T cell subsets over time

Subsets of T cells (CD4, CD8, Treg, Tnaive, Tcm, Tem, Te) from blood and bone marrow at various time points prior to and throughout treatment will be determined by multicolor flow cytometric analysis. The anatomical distribution of Treg, CD8, CD4 T cells in relationship to leukemic blasts in the bone marrow will also be determined by immunohistochemistry.

9.2.2 PD-1, TIM 3, and LAG1 expression over the course of treatment on subsets of T cells

Quantitation of PD-1, and other immune inhibitory molecules such as TIM 3, and LAG1 expression levels on different subsets of T cells (CD4, CD8, Treg, Tnaive, Tcm, Tem, Te) will be determined by flow cytometric analysis prior to and at various time points throughout study treatment. The results will be analyzed in reference to disease response.

9.2.3 PDL1 and CD19 expression on leukemic blasts and normal B cells

Quantitation of CD19 and PDL1 expression levels on ALL cells and normal B cells will be determined by flow cytometry methods such as the QuantiBrite bead analysis prior to and at various time points throughout study treatment. PD-L1 expression will also be measured by immunohistochemistry performed on formalin-fixed, paraffin-embedded bone marrow core samples before and during treatment. These results will be analyzed in reference to disease response.

9.2.4 Cytokine analysis

Research participants will have peripheral blood draws and bone marrow studies as described in the study calendars until study completion. These will be analyzed for the presence of cytokines such as GM-CSF, IFN-γ, IL-2, IL-6, IL-10, IL-12, TNF-α, and VEGF, using the Human Cytokine 30-Plex Luminex assay (Invitrogen).

9.2.5 TCR repertoire analysis

DNAs from enriched T cells from peripheral blood and or bone marrow prior to and at various time points during treatment will be subjected to ImmunoSEQ or ClonoSEQ (Adaptive Biotechnologies) analysis for detection of any preferential TCR clonal expansion upon treatment and

9.2.6 Leukemic cell clonality analysis

DNAs from enriched leukemic cells from bone marrow prior to and at various time points during treatment will be subjected to ImmunoSEQ (Adaptive Biotechnologies) analysis for detection of the evolution of B cell clonalities before and after treatment.

9.2.7 Gut microbiota profiling

All microbiota analyses will be performed according to published methods by COH/TGen Microbiome Core at TGen North, TGen's Flagstaff, AZ campus. DNA will be extracted from stool samples using commercially available kits, such as ZR fecal DNA MicroPrep kit (Zymo Research). Extracted DNA will be stored at -20°C. 16S rRNA gene will be amplified by PCR as follows:

16S rRNA amplification: The V4 region of the bacterial 16S rRNA gene will be amplified from each total DNA sample using bacterial/archaeal primers 515F (5′-GTGCCAGCMGCCGCGGTAA-3′) and 806R (5′-GGACTACHVGGGTWTCTAAT-3′), as previously described by Caporaso et al.73 Polymerase chain reaction (PCR) will be performed in a volume of 25 µL using the TaKaRa ExTaq enzyme mixture (Takara Bio, Inc., Shiga, Japan) and 200 ng of fecal DNA. The cycling conditions were as follows: initial denaturation at 94°C for 3 min, followed by 25 cycles of 94°C for 45 s, 50°C for 1 min, and 72°C for 1min, and a final extension at 72°C for 10 min. The PCR products will be stored at 4°C. Equal quantities of each sample will be pooled, and the PCR products will be gel-purified and sequenced by MiSeq (Illumina) according to the manufacturer’s protocol. Reads will be demultiplexed using the Illumina software.

9.2.8 Other potential analyses

Any biomarker sample collected according to the Study Calendar (Section 10) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability. The investigators also reserve the right to adjust the studies to be performed as techniques evolve and new information may become available that is relevant to the study agent and/or study population.

10 Study Calendar

Examination[A]	**Screening**	**Cycle 1 (Schedule A 35 days/Schedule B 42 days)**									**Cycles 2-5 (42 days each)**						**SFU Visit**	**LTFU[M] (to 1 yr)**
Day (D)	D-28 to D0	D1	D7	D8	D9	D15 ±1	D22 ± 1	D29 ± 1	D35 - 3	Sch B D36 ± 1	D1	D8 ± 1	D15 ±1	D22 ± 1	D29 ± 1	D36 ± 1	30 days after last dose (+ 7 days)	Every 3 months (±2 wks)
Informed consent	X																	
Medical history /demographics	X																	
Eligibility Criteria	X																	
Registration	X																	
Physical examination	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X [M2, M3 optional]
Vital signs[B]	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X [M2, M3 optional]
ECOG	X	X		X		X	X	X		X	X	X	X	X	X	X	X	X [M2, M3 optional]
Neurological examination	X	X		X		X	X	X		X	X	X[O]	X[O]	X[O]	X[O]	X[O]	X	
MMSE[C]	X	X		X		X	X	X		X	X[C]	X[C]	X[C]	X[C]	X[C]	X[C]	X	
Microbiome[Q]	X[Q]					X[Q] Sched A	X[Q] Sched B		X[Q] Sched A	X[Q] Sched B						X[Q] Cycle 2		
Lumbar Puncture/ CNS prophylaxis[D]	X[D]							X[D] Sched A		X[D] Sched B					X[D]			X[D, M2, M3]
Bone Marrow aspirate/biopsy[E]	X							X[E] Sched A		X[E] Sched B					X[E]		X[E]	X [M2, M3]
CBC with differentials	X	X		X		X	X	X		X	X			X		X	X	X [M2, M3]
CMP	X	X		X		X	X	X		X	X			X		X	X	X [M2, M3]

Examination[A]	**Screening**	**Cycle 1 (Schedule A 35 days/Schedule B 42 days)**									**Cycles 2-5 (42 days each)**						**SFU Visit**	**LTFU[M] (to 1 yr)**
Day (D)	D-28 to D0	D1	D7	D8	D9	D15 ±1	D22 ± 1	D29 ± 1	D35 - 3	Sch B D36 ± 1	D1	D8 ± 1	D15 ±1	D22 ± 1	D29 ± 1	D36 ± 1	30 days after last dose (+ 7 days)	Every 3 months (±2 wks)
+ uric acid, LDH, phos, mag																		
PT/INR/PTT	X	X						X		X	X					X	X	
IgG[F]		X						X		X	X					X	X	
Complete Urinalysis	X	X									X						X	
Creatinine Clearance[G]	X																	
Thyroid function[H] (T3/FT3, FT4, TSH)	X	X									X Cycle 3						X	X [M2, M3]
Urine Pregnancy Test	X																X	
HIV/HBC/HCV	X																	
Pulmonary Function Test	X																	
ECG[S]	X										X[S]							
Echo or MUGA	X																	
Biomarker Blood Sample[I]		X		X		X	X	X		X						X		
Required hospitalization		Day 1-9 minimum				Day 15-16												
Pembrolizumab Dosing[J]						Sch A	Sch B				X			X				
Blinatumomab Dosing[K]		9 µg continuous infusion		28 µg continuous infusion							28 µg continuous infusion							28 µg per SOC schedule[N, M2]

Examination[A]	**Screening**	**Cycle 1 (Schedule A 35 days/Schedule B 42 days)**									**Cycles 2-5 (42 days each)**						**SFU Visit**	**LTFU**[M] **(to 1 yr)**
Day (D)	D-28 to D0	D1	D7	D8	D9	D15 ±1	D22 ± 1	D29 ± 1	D35 - 3	Sch B D36 ± 1	D1	D8 ± 1	D15 ±1	D22 ± 1	D29 ± 1	D36 ± 1	30 days after last dose (+ 7 days)	Every 3 months (±2 wks)
Writing Test[L]		Continuously throughout the study									Continuously throughout the study							
AE/SAE Assessment	X	Continuously throughout the study									Continuously throughout the study						X	X [M2, M3]
Concomitant Medications	X	Continuously throughout the study									Continuously throughout the study						X	X[P, M2, M3]
Survival		Continuously throughout the study									Continuously throughout the study						X	X[M1, M2, M3, M4]

[A] All procedures completed on day 1 must be completed prior to the initiation of study treatment. Assessment should be performed on specified day of each treatment cycle unless stated via a footnote.
[B] Vital signs include height and weight, but height is performed before first dose at baseline only.
[C] Mini Mental Status Exam (MMSE; **Appendix 18.4**) is completed weekly on days 1, 8, 15, 22, 29, 36 (Schedule B) of the first cycle. MMSE as clinically indicated after cycle 2. MMSE also completed at SFU visit.
[D] Lumbar puncture /CNS prophylaxis within 2 weeks (±3 days) prior to start of therapy AND as needed for SOC disease staging (day 29-36) along with bone marrow study. IT chemotherapy is allowed for CNS prophylaxis per treating physician recommendation in between cycles throughout the study.
[E] Screening BM needed only if BM aspirate was not performed as part of standard care and a sample was not provided for hematological and MRD assessment. Additional bone marrow biopsy samples will be collected in 2 x 6 ml lavender EDTA tubes (Section 9.1) for research biomarker assays during SOC collections. Bone marrow aspirates will be collected at the end of cycle 1 between 3 to 7 days before start of cycle 2. For subsequent cycles (2+), bone marrow aspirates will be collected 1 to 14 days before start of next cycle (between days 29 and 42) at SOC marrow collection times until CR is documented (first of 2 consecutive leukemia-free biopsies). After CR is attained, biopsies for patients remaining on treatment will be within 2 weeks of the end of every other cycle up to cycle 5. Bone marrow aspirate/biopsy is optional at the safety follow-up visit (SFU). If a subject has not relapsed or gone onto allogeneic hematopoietic stem cell transplant (alloHSCT) by the end of their last treatment cycle, bone marrow aspirate should be performed every 3 months until relapse or progression.
[F] Immunoglobulin (IgG) level will be determined before the first dose at baseline, at the end of each cycle, and the SFU visit.
[G] Calculated creatinine clearance only required if screening creatinine is >1.5 ULN.
[H] TSH will be tested approximately at screening and at beginning of Cycles 1 and 3, and every 3 months during patients being seen in LTFU
[I] Biomarker samples: one 35 ml –blood draw (in one x 6 ml red top serum tube and five x 6 ml lavender top EDTA tubes) is to be collected weekly at cycle 1 day 1 prior to blinatumomab dose, days 8, 15, 22, 29 day 36 ± 1 day (Schedule B),) and 36 ± 1 day of each subsequent cycle.
[J] Pembrolizumab is given on day 15 during cycle 1 for patients on Schedule A. Pembrolizumab is given on day 22 during cycle 1 for patients on Schedule B. Pembrolizumab is given on days 1 and 22 cycle 2 and thereafter for both schedules.
[K] Blinatumomab dosing will be 9 µg/kg continuous iv for the first 7 days of treatment, then steps up to 28 µg/kg continuous iv on day 8 for the remainder of treatment.

[L] Subject writing test (**Appendix 18.3**) completed in the morning and evening on days 1 and 2 of each cycle, daily for the rest of cycle 1, then once weekly at scheduled clinic visits cycles 2-4.

[M] Assessments in this column are applied depending on the type of additional treatment after completion of protocol therapy as described in Section 5.10 Follow-Up.

[M1] For patients who have undergone alloHSCT, transplant data from CIBMTR forms/COH transplant registry will be utilized as described in Section 5.10.2.1.

[M2] For participants in CR who have completed the prescribed 5 cycles of treatment or have discontinued pembrolizumab after cycle 1 due to intolerability, who continue receiving blinatumomab as a single agent, follow up assessments and visits are described in Sections 5.10.2.2.

[M3] For patients in CR who have completed the prescribed 5 cycles of treatment, are ineligible for or decline alloHSCT, and are intolerant to or opt against blinatumomab treatment, follow up assessments and visits are described in Section 5.10.2.3.

[M4] Subjects who did not respond to or have relapsed after treatment, and are being followed in long-term follow-up (LTFU), will only undergo a telephone contact to determine survival status by the study team or treatment physician (Section 5.10.3).

[N] Blinatumomab will be allowed as a single agent for up to 8 cycles (total of up to 9 cycles of blinatumomab per SOC) according to the schedule in the blinatumomab prescribing information, for patients who complete treatment in CR/CRi (or have discontinued pembrolizumab after cycle 1 due to intolerability) and are ineligible for or decline transplant.

[O] Neurological Exam is optional after cycle 2 and to be given only as clinically indicated.

[P] Concomitant medication documentation during LTFU period is limited to only anti-leukemic treatments. For patients remaining on blinatumomab, concomitant meds will be recorded with start and stop dates and indication only. For patients going to alloHSCT, medications will be collected that are part of the conditioning regimen and the GVHD prophylaxis regimen, pulled from the CIBMTR forms/COH transplant registry

[Q] Microbiome (i.e. stool) sample pretreatment to be provided within 1 week of treatment start, in cycle 1 on day 15 (- 3 days) for Schedule A or on day 22 (-3 days) for Schedule B microbiome sample to be provided prior to pembrolizumab dosing. Microbiome sample to also be provided at the end of cycle 1 on day 35 (-3 days) for Schedule A or on day 36 (+6 days) for Schedule B and at the end of Cycle 2 on day 36 (+6 days).

[R] A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically important by the Investigator. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history. If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout or run-in treatment).

[S] Repeat 12-lead ECG performed during screening and on day 1 of cycles 2 and 5.

11 Study Endpoints

11.1 Primary Endpoint: Phase 1

The primary endpoint is toxicity (secondary endpoint for phase 2 portion). Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) version 5. Dose limiting toxicity (DLT) is defined in **Section 5.3** of the protocol. The DLT evaluation period will be from the start of treatment through the end of the first cycle, so: 35 days for Schedule A, and 42 days for Schedule B.

The maximum tolerated schedule will be based on the assessment of DLT during cycle 1. The recommended phase 2 schedule (RP2S) will be selected based on maximum tolerated schedule and a review of cumulative toxicity and tolerability data (after cycle 1) and may be lower than the maximum tolerated schedule. All patients who are not evaluable for DLT will be replaced.

11.2 Primary Endpoint: Phase 2

The primary endpoint is response (CR/CRi), which will be assessed/recorded at the end of each cycle until disease progression/recurrence or end of treatment. We will then determine best response for each patient during the trial active treatment period.

Response will be based on the NCCN guidelines on ALL version 1 2017 response criteria [43] in **Appendix 18.8**.

11.3 Secondary Endpoints (All Evaluable Patients):

Toxicity (Phase 2 enrollment only): Toxicity will be graded according to the NCI-CTCAE version 5. Unacceptable toxicity (UT) shares the same definition as DLT (**Section 5.3**) of the protocol. The UT evaluation period will be from the start of treatment through the end of the first cycle, so: 35 days for Schedule A, and 42 days for Schedule B.

Duration of Remission: Defined as the time interval from the date of first documented response (CR/CRi) to documented disease relapse, progression or death whichever occurs first.

Time to Response: Defined as the time interval from date of first dose of study drug to first documented response (CR/CRi).

Overall Survival: Defined as the time interval from date of first dose of study drug to date of death from any cause.

Event-Free Survival: Defined as the time interval from date of first dose of study drug to first documented disease relapse, progression or death from any cause, whichever occurs first.

Allogeneic HSCT: Number of cycles of therapy completed prior to alloHSCT.

Cycles completed: Number of cycles of combination and single agent(s) completed.

Minimal residual disease rate: number and proportion of patients with CR who have confirmed minimal residual disease.

12 Statistical Considerations

12.1 Study Design

This study will be conducted as a single center, open-label, phase 1/2 clinical trial.

The study is designed to evaluate the safety and anti-leukemia activity of pembrolizumab when combined with blinatumomab as part of a 5 or 6-week treatment cycle (Schedule A or B). The anti-leukemia activity of the combination therapy, among patients treated at the recommended phase 2 schedule will also be assessed. In both Schedules A and B, the pembrolizumab (200mg) and blinatumomab doses (28 µg/day) are fixed except that blinatumomab is given at 9 µg/day on days 1 to 7 during cycle 1.

12.1.1 Phase 1:

The phase 1 portion of the trial will implement traditional '3+3 rules' for enrollment, with schedule 'reduction' (from Schedule A to Schedule B) or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs) during cycle 1. Up to two schedules will be tested.

Schedule[+]	Cycle Length	Pembrolizumab: 200mg	Blinatumomab: 28 µg/day† CIV
A (starting schedule)	35 days cycle 1, 42 days cycles 2–5	cycle 1#: day 15 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28
B*	42 days all cycles	cycle 1: day 22 cycles 2-5: day 1 and 22	cycles 1-5: days 1 to 28

[+]: Enrolled patients may receive up to 5 cycles of treatment.
*: While it is believed that Schedule A will be well tolerated, one schedule 'reduction' is allowed, from Schedule A to Schedule B, in the presence of dose limiting toxicity. Under Schedule B, during cycle 1, initiation of pembrolizumab is delayed by 7 days and the treatment free interval is extended to 14 days.
#: The length of cycle 1 in Schedule A is 35 days. All other cycles in Schedules A and B are 42 days.
†: In cycle 1, on days 1-7, blinatumomab will be given at 9 µg/day.

Depending on schedule assignment, the first cycle will be either 35 days (Schedule A) or 42 days (Schedule B). After Cycle 1, on both schedules patients will be treated in planned 42-day treatment cycles until disease relapse, progression, unacceptable toxicity, or other criteria for removal from study treatment are satisfied. Patients will undergo response evaluation using the ALL response criteria v01.2017 (see Section 11.2) at the end of each cycle.

The schedule that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated schedule. The recommended phase 2 schedule of pembrolizumab/blintumomab will generally be the same as the maximum tolerated schedule, but it may be less than the maximum tolerated schedule based on a review of available data/cumulative toxicities. Once the maximum tolerated schedule/ recommended phase 2 schedule has been determined the phase 2 study of the combination will be initiated.

12.1.1.1 Schedule B (if necessary)

Up to six subjects may be treated with delayed initiation of pembrolizumab 200 mg during cycle 1.

Pembrolizumab will be omitted during the first 3 weeks of cycle 1 and start on day 22. If the rate of DLT after 1 cycle of the combination treatment, is <33% (<2/6 subjects), the recommended phase 2 schedule of prembrolizumab will be 200 mg every 3 weeks starting on day 22 of cycle 1 and the study will advance to the phase 2 part of the study. If DLT occurs in ≥33% of subjects (≥2/6), the study will be discontinued due to unacceptable toxicity of this drug combination.

12.1.1.2 Schedule Reduction/Expansion:

DLT incidence will be based on toxicity events encountered during the first cycle of treatment.

Schedule 'reduction' (from Schedule A to Schedule B) or cohort expansion will only take place after 3 patients are fully assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 5 following the completion of cycle 1.

Schedule reduction/expansion will occur according to the following rules:

Schedule Reduction/Expansion Rules	
# of patients with DLT on a given Schedule	**Decision Rule**
0 out of 3	Enter 3 more patients, for a total of 6.
≥2 out of 3 or ≥2 out of 6	If Schedule A: Enter 3 patients on Schedule B. If Schedule B: terminate enrollment.
1 out of 3	Enter 3 more patients, for a total of 6.
0 out of 6 or 1 out of 6	If Schedule A or B, this schedule will be declared the maximum tolerated schedule. Note: At least 6 patients must be entered at the maximum tolerated schedule.

12.1.2 Phase 2:

The phase 2 portion will implement a Simon two-stage optimal design (Simon 1989; Jung 2004) to evaluate the anti-leukemia activity of the two agent combination as assessed by overall response (CR, CRi) rate, in patients with relapsed/refractory ALL. The study is expected to enroll and treat a minimum of 12 and a maximum of 30 patients at the recommended phase 2 schedule. The sample size is based on the desire to discriminate a promising CR/CRi rate of 64% from a disappointing response rate of 44% (from blinatumomab single-agent TOWER trial (Kantajarian et al. 2017 [16]) using a type I error rate of 0.10 and power of 80%. At stage 1, 12 patients will be entered on the study. Note: The six patients treated at the recommended phase 2 schedule in the phase 1 portion of the study will count toward the 30 patients required; given this, we expect to enroll only 24 new patients on the phase 2 trial. If ≤ 5 complete remissions are seen, the study will be terminated. If at least 6 patients achieve CR/CRi, the trial will continue to the second stage. At stage 2, 18 additional patients will be entered. At the end of stage 2, if 17 or more patients experience complete remission, the combination will be considered worthy of further study. If ≤ 16 patients experience a complete remission then no further investigation of the combination is warranted.

As of 12/10/2024, a total of 25 subjects have been accrued, with 23 response evaluable. Out of these 23 evaluable subjects, 17 have achieved complete remission (CR) already. Since the target success threshold 17 CR/CRi has been accomplished, and also considering the slow accrual of blinatumomab-naive patients, we are planning to accrue just one more subject and close the study. Therefore, we will end up with a total of 26 accruals, including 23-24 evaluable subjects (6 from phase 1 portion, plus 17-18 from phase 2 portion).

12.1.3 Stopping Rules for Unacceptable Toxicity:

Note: The same criteria for DLT in **Section 5.3** will be used to define unacceptable toxicity during the phase 2 portion of the trial.

The following table will be consulted as relevant toxicities are encountered following the phase 1 study. The early stopping rule for safety/toxicity will be assessed for each patient at the end of cycle 1. The expected rate of unacceptable toxicity should not be ≥33%. See the table below for detailed early stopping rules. Patients with ongoing toxicity (beyond cycle 1) will be followed until resolution or stability. If more than the specified number of patients has significant treatment related toxicities, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee will be mandated. Patient accrual will not resume until approved by the Data Safety Monitoring Committee and the Leukemia Disease Team to do so.

	# of patients with unacceptable	Cumulative probability of early stopping given a toxicity rate of:

# of patients treated at phase 2 dose	toxicity to halt enrollment	15%	33%	45%
6	2	0.22	0.64	0.84
12	4	0.24	0.73	0.92
18	6	0.25	0.78	0.95
24	8	0.25	0.81	0.97

In addition, any death, regardless of attribution, will trigger a review by two COH leukemia specialists (besides the study PI) for formal/final attribution determination. The result will be documented in the comments section of the AE log in RAVE for events considered contributing to the death event. Any death, that ultimately is determined to be attributable to study treatment, will require that the entire study be placed on hold and the study team will discuss with pharmaceutical partners regarding a new dose modification plan. After consideration by the study team (study PI[s], statistician, etc.) and DSMC, a decision will be made as to whether accrual/treatment can be resumed safely or whether protocol modifications are necessary.

12.2 **Demographic Data and Baseline Characteristics**

The number and percentage of subjects screened, allocated, the primary reason for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g. age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized using descriptive statistics.

12.3 **Efficacy Analysis**

Overall response rate (patients that have confirmed CR/CRi) and 95% Clopper Pearson binomial confidence interval (CI) will be calculated. In addition, sub-analyses will be performed where participants will be considered evaluable for response if they are confirmed eligible, receive at least 50% of both agents during the first cycle of therapy and have their disease re-evaluated. Remission rates will also be explored based on number/type of prior therapy(ies). Time to response and progression and overall survival will be estimated using the product-limit method of Kaplan and Meier.

12.4 **Safety Analysis**

All participants will be evaluable for toxicity if they receive any study treatment. Participants will be considered evaluable for schedule expansion/reduction if they receive at least 50% of both agents of the study treatment and are followed during cycle 1 or experience a DLT. All participants who are not evaluable for schedule expansion/reduction will be replaced. Note: While patients who receive <50% of the intended dose of the study treatment will be considered inevaluable for determination of maximum tolerated schedule, if a patient discontinues treatment due to toxicities prior to receiving 50% of the dose, the patient will be considered evaluable and will not be replaced. Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, attribution, time of onset, duration, probable association with the study treatment and reversibility or outcome. Baseline information (e.g. the extent/type of prior therapy). The recommended phase 2 schedule will most likely be the maximum tolerated schedule, but may be lower and will be consider cumulative toxicity data and patient tolerability, including toxicities occurring after the DLT period.

12.5 **Correlative Studies of Microbiome Diversity**

Gut microbiome diversity will be estimated/assessed using the inverse Simpson index (Taur et al 2014) at each time point of stool sample collection: baseline, prior to pembrolizumab administration, the end of cycles 1 and 2. The trend of change in the inverse Simpson index from baseline will be visualized

graphically as continuous and repeated measurements. Linear mixed models will be used to compare the over-time change in the index between responders and non-responders, or between patients of high- vs low- grade toxicities. Patients will also be classified into high (>4), intermediate (2-4), and low (<2) diversity groups in terms of the baseline inverse Simpson index. The association between the categorized microbiome diversity and response or toxicity will be assessed by Fisher exact test. The association between the baseline microbiome diversity groups and clinical outcomes, such as response duration, EFS and OS, will be assessed by estimating and comparing the event (progression, relapse, death, etc.) rate between the three index groups using Kaplan-Meier method and log-rank test (when the group size is allowed). Associations between other biomarkers, such as T cell subsets, serum cytokine concentrations, PD-L1 expressions, and clinical outcomes will be assessed similarly as above.

12.6 **Sample Size**

Number of Evaluable Patients: 23-24

Phase 1: 6-12* (expected)

Phase 2: 17-18* (expected)

*: The six patients treated at the recommended phase 2 schedule (RP2S) in the phase 1 portion of the study will count toward the 23-24 evaluable patients required; given this, we expect to enroll only 17-18 extra evaluable patients on the phase 2 trial.

If taking into account the expected 10% inevaluable rate, the total accruals may be up to 26.

Accrual for both phases is expected to be completed in 73 months. Patients may receive up to 5 cycles of therapy and will be followed for 1 year following start of study treatment. The expected maximum follow-up/study duration is 85 months.

12.7 **Timing of Analyses**

Efficacy analysis will be performed at the end of study treatment.

13 Data Handling, Data Management, Record Keeping

13.1 **Source Documents**

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 **Data Capture Methods and Management**

Data for this trial will be collected using City of Hope's electronic capture system that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 **Case Report Forms/Data Submission Schedule**

The Investigator is responsible for all information collected on participants enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel.

The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	**Phase 1**: Within 7 calendar days of the assessment/notification **Phase 2**: Within 10 calendar days of the assessment/notification
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

13.4 Regulatory Records

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14 Adherence to the Protocol & Reporting of Protocol Deviations

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

14.1 Reporting by COH

All protocol deviations and planned protocol deviations will be reported in accordance with the Clinical Research Protocol Deviation policy.

14.2 Reporting by non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the DCC and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet or submit your site-specific protocol deviation log if the log format has been approved for use by the DCC. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet or protocol deviation log to the Study PI (ebudde@coh.org) and DCC@coh.org within 24 hours of notification of the deviation with the email subject title of "Blina/Pembro for B-cell ALL Deviation COH IRB #19017". If an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

3. Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

15 Study Oversight, Quality Assurance, and Data & Safety Monitoring

15.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

15.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

15.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AEs/UPs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

15.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

15.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because the study involves a COH IND.

15.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety and accrual data from this trial via the PMT Progress Report (submitted by

the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.
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16 Ethical and Regulatory Considerations

16.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

16.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17

16.3 Institutional Review Board

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information

that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the PI, will require review and approval by the COH IRB before the changes are implemented in the study.

All participating sites must follow the lead institution's IRB-approved protocol.

16.4 **Recruitment of Subjects**

Research participants will be identified through the clinical practices of the PI, co-PIs and participating clinicians and through direct referrals from outside hospitals and physicians. No direct-to-patient advertising will be performed without IRB approval.

16.5 **Informed Consent Processes**

Each participating non-COH institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Research subjects will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope/participating institution or any relationship they have with City of Hope/participating institution. Research subjects will be afforded sufficient time to consider whether or not to participate in the research.

Should sufficient doubt be raised regarding the adequacy of comprehension, further clarifications will be made and the questionnaire repeated until a satisfactory result is obtained. Prospective research subjects who cannot adequately comprehend the fundamental aspects of the research study with a reasonable amount of discussion, education and proctoring will be ineligible for enrollment. For those subjects who do comprehend the fundamental aspects of the study, consent will be obtained and documented, followed by eligibility testing. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements. The research team will review the results of eligibility testing and determine if the subject is a candidate for study enrollment.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the site investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

16.6 **Confidentiality**

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed participant authorization informing the

participant of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

Source documents provided to COH by participating sites for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring/ auditing, IRB reviews, and FDA/regulatory authority inspections. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Biospecimens will be de-identified (coded) prior to submission to internal and external research laboratories. The coded identifier will be the C OH research patient number (RPN) provided by the COH clinical trial management system, which is devoid of direct participant identifiers. The key to the code is maintained in the C OH clinical trial management system which is a secure environment.

16.7 **Special and Vulnerable Populations**

16.7.1 Inclusion of Women and Minorities

The study is open anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the effects of study agent(s) on embryogenesis, reproduction, and spermatogenesis in humans are unknown.

16.7.2 Exclusion of Pediatric Population

Pediatric participants (< 18 years old of age) are excluded from this study since safety and effectiveness of protocol therapy has not been defined for the study population. Additional studies may be performed in the pediatric population once safety and effectiveness of protocol therapy is defined in the adult study population.

16.7.3 Inclusion of HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

16.7.4 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

16.8 Use of Unused (Leftover) Specimens Collected for this Trial

In the informed consent, the participant asked to indicate how he or she would like any remaining unused samples in existence at the study completion. The options include: (a) placing the samples in a COH IRB approved biorepository with some clinical information and potentially PHI attached, (b) fully de-identifying the samples (prior to study completion) so that they may be used for research that is exempt from IRB review, or (c) having the samples destroyed.

While it is the intent to achieve the selected option, to best protect the participant, if option of "a" or "b" is selected and is not feasible at the time of study completion, the participant's leftover samples will be destroyed before completion to best protect their interest.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would be communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

16.9 Financial Obligations and Compensation

The investigational drug, pembrolizumab, will be provided free of charge by Merck & Co. Blinatumomab will be obtained from commercial supply as standard of care.

The standard of care drug(s) or device(s) and procedures provided will be the responsibility of the research participant and/or the insurance carrier. The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study. However, neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope/non-COH site to the injured research participant, however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

16.10 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope and Merck and Amgen, and participating non-COH institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

17 References

1. Pui, C.H. and W.E. Evans, *Acute lymphoblastic leukemia.* N Engl J Med, 1998. **339**(9): p. 605-15.
2. Jabbour, E.J., S. Faderl, and H.M. Kantarjian, *Adult acute lymphoblastic leukemia.* Mayo Clin Proc, 2005. **80**(11): p. 1517-27.
3. *SEER Cancer Statistics Review, 1975-2009, National Cancer Institute*. 2012 [cited June 2015; Available from: http://seer.cancer.gov/archive/csr/1975_2009_pops09/.
4. Kantarjian, H.M., et al., *Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration.* Cancer, 2010. **116**(24): p. 5568-74.
5. Advani, A.S., et al., *Southwest Oncology Group Study S0530: a phase 2 trial of clofarabine and cytarabine for relapsed or refractory acute lymphocytic leukaemia.* Br J Haematol, 2010. **151**(5): p. 430-4.
6. O'Brien, S., et al., *Outcome of adults with acute lymphocytic leukemia after second salvage therapy.* Cancer, 2008. **113**(11): p. 3186-91.
7. O'Brien, S., Aulitzky W, et al., *Phase II study of marqibo in adult patients with refractory or relapsed Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL).* Journal of Clinical Oncology, 2010. **28**(15s).
8. Duval, M., et al., *Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure.* J Clin Oncol, 2010. **28**(23): p. 3730-8.
9. Tavernier, E., et al., *Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial.* Leukemia, 2007. **21**(9): p. 1907-14.
10. Dreier, T., et al., *Extremely potent, rapid and costimulation-independent cytotoxic T-cell response against lymphoma cells catalyzed by a single-chain bispecific antibody.* Int J Cancer, 2002. **100**(6): p. 690-7.
11. Loffler, A., et al., *A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes.* Blood, 2000. **95**(6): p. 2098-103.
12. Wolf, E., et al., *BiTEs: bispecific antibody constructs with unique anti-tumor activity.* Drug Discov Today, 2005. **10**(18): p. 1237-44.
13. *Blinatumomab Investigator's Bronchure*. Amgen Inc: Thousand Oaks, CA.
14. *Blincyto (R) [package insert]* 2014.
15. Topp, M.S., et al., *Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study.* Lancet Oncol, 2015. **16**(1): p. 57-66.
16. Kantarjian, H., et al., *Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia.* New England Journal of Medicine, 2017. **376**(9): p. 836-847.
17. Disis, M.L., *Immune regulation of cancer.* J Clin Oncol, 2010. **28**(29): p. 4531-8.
18. Dudley, M.E., et al., *Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma.* J Clin Oncol, 2005. **23**(10): p. 2346-57.
19. Hunder, N.N., et al., *Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1.* N Engl J Med, 2008. **358**(25): p. 2698-703.
20. Greenwald, R.J., G.J. Freeman, and A.H. Sharpe, *The B7 family revisited.* Annu Rev Immunol, 2005. **23**: p. 515-48.

21. Okazaki, T., et al., *PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine.* Proc Natl Acad Sci U S A, 2001. **98**(24): p. 13866-71.
22. Zhang, X., et al., *Structural and functional analysis of the costimulatory receptor programmed death-1.* Immunity, 2004. **20**(3): p. 337-47.
23. Chemnitz, J.M., et al., *SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation.* J Immunol, 2004. **173**(2): p. 945-54.
24. Sheppard, K.A., et al., *PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta.* FEBS Lett, 2004. **574**(1-3): p. 37-41.
25. Riley, J.L., *PD-1 signaling in primary T cells.* Immunol Rev, 2009. **229**(1): p. 114-25.
26. Parry, R.V., et al., *CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms.* Mol Cell Biol, 2005. **25**(21): p. 9543-53.
27. Francisco, L.M., P.T. Sage, and A.H. Sharpe, *The PD-1 pathway in tolerance and autoimmunity.* Immunol Rev, 2010. **236**: p. 219-42.
28. Agata, Y., et al., *Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes.* Int Immunol, 1996. **8**(5): p. 765-72.
29. Vibhakar, R., et al., *Activation-induced expression of human programmed death-1 gene in T-lymphocytes.* Exp Cell Res, 1997. **232**(1): p. 25-8.
30. Nishimura, H., T. Honjo, and N. Minato, *Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice.* J Exp Med, 2000. **191**(5): p. 891-8.
31. Brown, J.A., et al., *Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production.* J Immunol, 2003. **170**(3): p. 1257-66.
32. Sharpe, A.H. and G.J. Freeman, *The B7-CD28 superfamily.* Nat Rev Immunol, 2002. **2**(2): p. 116-26.
33. Thompson, R.H., et al., *PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma.* Clin Cancer Res, 2007. **13**(6): p. 1757-61.
34. Nomi, T., et al., *Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer.* Clin Cancer Res, 2007. **13**(7): p. 2151-7.
35. Gao, Q., et al., *Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma.* Clin Cancer Res, 2009. **15**(3): p. 971-9.
36. Hamanishi, J., et al., *Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer.* Proc Natl Acad Sci U S A, 2007. **104**(9): p. 3360-5.
37. Fourcade, J., et al., *PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients.* J Immunol, 2009. **182**(9): p. 5240-9.
38. Merck & Co., I., *Pembrolizumab Investigator's Bronchure version 18*. 2020: Whitehouse Station, NJ.
39. *KEYTRUDA® (pembrolizumab) injection, for intravenous use*. 2020 January; Available from: https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.
40. Ansell, S.M., et al., *PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma.* New England Journal of Medicine, 2015. **372**(4): p. 311-319.

41. Moskowitz CH, R.V., Michot JM, et al. *PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: preliminary results from a phase 1b study (KEYNOTE-013)*. in *56th Annual Meeting of the American Society of Hematology*. 2014. San Francisco, CA.

42. Duell J, D.M., Bedkel T, Mueller T, Rasche L, Dandekar T, Einsele H, Topp M. *Crucial Role of Regulatory T Cells in Predicting the Outcome of the T Cell Engaging Antibody Blinatumomab in Relapsed and Refractory B Precursor ALL Patients*. in *56th Annual Meeting of the American Society of Hematology*. 2014.

43. National Comprehensive Cancer Network. *NCCN Guidelines for Acute Lymphoblastic Leukemia, v1.2017*. NCCN Clinical Practice Guidelines in Oncology 2017 06/01/2017; Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#all.

18 Appendices

18.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

*As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

18.2 Registration Coversheet

COH IRB# 19017: A phase 1/2 trial of pembrolizumab in combination with blinatumomab in patients with relapsed/refractory acute lymphoblastic leukemia

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: (626)-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator Name:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
	PI/ Sub-Investigator:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity		Method of Payment:_____	
☐	Black	☐	Hispanic	Codes:	
☐	Caucasian	☐	Non-Hispanic	01 Private	06 Military or Veterans Adm. sponsored
☐	Asian	☐	Other_____	02 Medicare	07 Self-pay (no insurance)
☐	American Indian			03 Medicare & private ins.	08 No means of payment (no insurance)
☐	Native Hawaiian/Pacific Islander			04 Medicaid	09 Unknown
☐	Other_____			05 Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

18.3 **Writing Test**

Patient ID_____

Instructions for the Patient: Enter the date and time of the test. Rewrite the phrase listed.

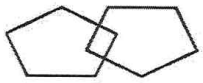
Study Day	Date	Time	***Sweet as apple pie***	Study Staff Initial and Date

18.4 **Mini Mental Status Exam (MMSE) Form**

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

Instructions: Score one point for each correct response within each question or activity.

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then the instructor asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

18.5 **Correlative Tissue Form (For All Sites)**

A copy of this form should accompany the sample shipments to COH Hematopoietic Tissue Biorepository.

Non-COH sites: refer to **Appendix 18.6** for shipping instructions to COH Hematopoietic Tissue Biorepository.

COH IRB number: 19017	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

18.6 FECAL SAMPLE COLLECTION INSTRUCTIONS (TO BE INCLUDED IN FECAL COLLECTION KIT)

You have been provided a Fecal Swab Collection kit.

The collection kit includes the following items:

1. Disposable Gloves
2. A stool collection bowl (toilet hat), as pictured below.



3. A bio-specimen bag

4. A pre-labeled DNA/RNA Shield Fecal Collection Tube, as pictured below. The tube has already been labeled with your assigned subject ID. **Please DO NOT write your name on the label.**



In order to ensure the best results, please follow the instructions below.

You will need to collect **four different** stool samples during this study:

1. The **first** stool sample is to be collected up to 7 days **before** your study treatment on day 1 of treatment cycle 1.

2. The **second** stool sample is to be collected up to 3 days **before** your first pembrolizumab treatment in cycle 1.

3. A **third** stool sample will be collected up to 3 days **before** the end of cycle 1 treatment.

4. The **final** stool sample will be collected up to 3 days **before** the end of cycle 2 treatment.

To Collect a Stool Specimen:

1. Raise the toilet seat and place the stool collection container (toilet hat) on the back of toilet bowl. Place the toilet seat down.
2. Pass stool into the stool collection container. Do not urinate into the container.
3. Put the provided disposable gloves on before collecting the stool sample. Use the scoop on the lid of the tube to collect a pea size amount of stool. Do not touch the swab on the sides of the collection bowl or on any other surface. Carefully re-insert the scoop into the tube, screw to close and then shake to homogenize (10 seconds).
4. Write the date and time of collection on the label that is affixed to the tube. DO NOT write your name on the tube.
5. Dump the remaining stool in the toilet and flush. The stool collection bowl and the disposable gloves may be disposed in the regular trash. Wash your hands thoroughly with soap and water.
6. Store the collection tube in the bio-specimen bag at room temperature.
7. Return the sample to the study team within 24-72 hours of collection. This should correspond with your next study visit. Sample can be transported in the car without need for ice packs.

IMPORTANT: If for some reason you cannot make your scheduled appointment within 72 hours of the fecal collection, please contact your study site at (site to specify contact tel number) to make arrangements for return of the sample.

If you have any questions please call (site to specify contact tel number)

Thank you for your participation!


ZYMO RESEARCH
The Beauty of Science is to Make Things Simple
Don't let the sample go into the toilet
Collect stool into a clean container
Scoop a portion of the stool sample into the DNA/RNA Shield™ Fecal Collection Tube
Wash hands well

18.7 TISSUE SHIPPING GUIDLINES TO CITY OF HOPE HTB

These guidelines apply to non-COH sites only.

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Wednesday**. If this is not feasible, advance arrangements should be made with City of Hope Hematopoietic Tissue Biorepository (HTB; Lucy Ghoda; lghoda@coh.org).
2. Notify Dr. Budde (ebudde@coh.org) or designee and the City of Hope HTB (Lucy Ghoda; lghoda@coh.org) of impending shipment. To request a FedEx shipping label, email DCC@coh.org and indicate the planned shipment date.
3. **Stool samples** should be shipped via overnight FedEx within 72 hours following collection.
4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for delivery by 10:30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.
5. On the day of shipment, email Dr. Budde (mailto:ebudde@coh.org) and Dr. Lucy Ghoda (lghoda@coh.org) the sample shipment information and a sample manifest.
6. Ship samples with a **copy of the Correlative Tissue Form (Appendix 18.5)** and a **copy of the pathology report** to:

   Lucy Ghoda (or current recipient staff personnel AND laboratory address)
   COH Hematopoietic Tissue Biorepository
   2004 Kaplan Clinical Research Building
   City of Hope National Medical Center
   1500 E. Duarte Road
   Duarte, CA 91010-3000
   T: 626-218-2157
   Email: lghoda@coh.org

18.8 **NCCN guidelines on ALL version 1 2017 Response criteria[43]**

18.8.1 Response criteria for Blood and Bone Marrow

CR

- No circulating blasts or extramedullary disease
    - No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement
- Tri-lineage hematopoiesis (TLH) and <5% blasts
- Absolute neutrophil count (ANC) ≥1000/microL
- Platelets ≥100,000/microL
- No recurrence for 4 weeks

CR with incomplete blood count recovery (CRi)

- Meets all criteria for CR except platelet count and/or ANC

Refractory disease

- Failure to achieve CR at end of induction

Progression Disease (PD)

- Increase of at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease

Relapsed disease

- Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after CR

18.8.2 *Response Criteria for Lymphomatous Extramedullary Disease*

CT of neck/chest/abdomen/pelvis with IV contrast and PET/CT should be performed to assess response for extramedullary disease

- CR: Complete resolution of lymphomatous enlargement by CT. For patients with a previous positive PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative
- PR: >50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site
- PD: >25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site
- No Response (NR): Failure to qualify for PR or PD
- Relapse: Recurrence of mediastinal enlargement after achieving CR. For patient with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site