PROTOCOL TITLE

A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast percentage:
University of California Hematologic Malignancies Consortium Study #1504 (UCHMC1504)

Protocol: Amendment 9
Date: 3/17/2021

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University of California
Hematologic Malignancies Consortium
UCD UCI UCLA UCSD UCSF

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Study Agent: Blinatumomab, Pembrolizumab

IND Number: 134234

IND Holder: Matthew Wieduwilt, UC San Diego

Protocol	Date
Amendment 9	3/17/2021

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

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Participating Site Principal Investigator

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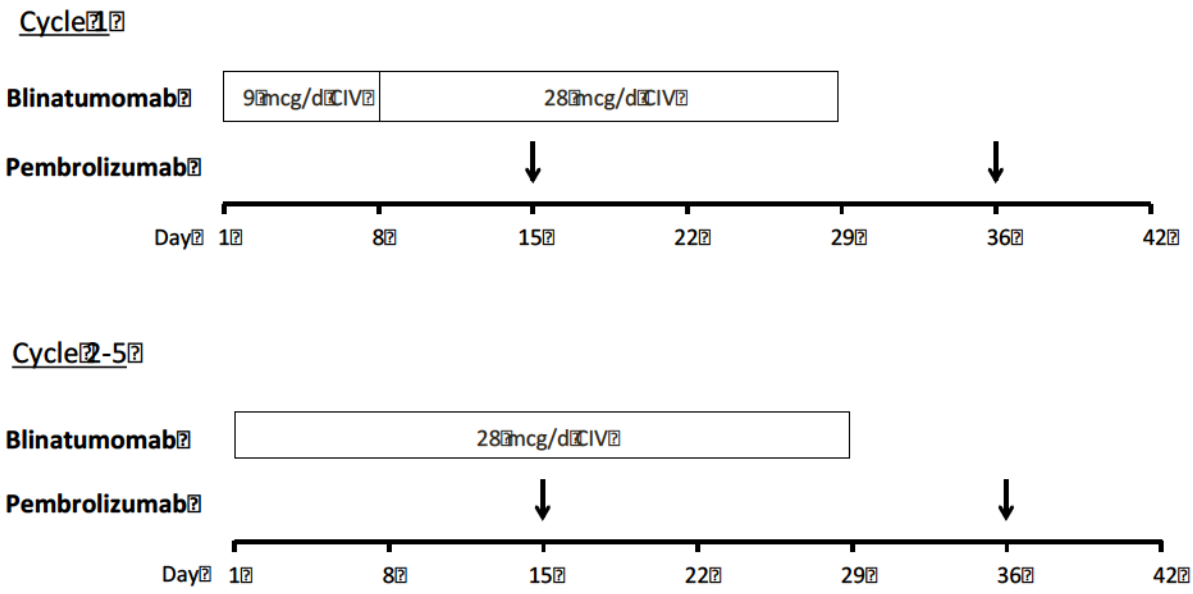
TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALL	Acute lymphoblastic leukemia
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CIV	Continuous Intravenous
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CRh	Complete Response with Partial Hematologic Recovery
CRi	Complete Response with Incomplete Count Recovery
CSF	Cerebrospinal fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
HIV	Human Immunodeficiency Virus
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
Ph	Philadelphia Chromosome
PMN	Polymorphonuclear
PO	per os/by mouth/orally
PR	Partial Response
PT	Prothrombin Time
RFS	Relapse-free Survival
SAE	Serious Adverse Event
SD	Stable Disease
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

UPR	Unanticipated Problems involving Risk to subjects or others
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia (ALL) with high bone marrow lymphoblast percentage: University of California Hematologic Malignancies Consortium study #1504 (UCHMC1504)
Short Title	Phase I/II study of blinatumomab with pembrolizumab for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia
Phase	I/II
Methodology	Phase I/II of blinatumomab in combination with pembrolizumab in adult patients with relapsed or refractory B-lineage ALL

Study Duration	48 months
Study Center(s)	Multi-center: UCSD, UCD, UCI,UCSF
Objectives	Primary: To determine if the addition of pembrolizumab to blinatumomab improves the overall response rate (CR+ CRh) relative to blinatumomab alone in adult subjects with relapsed or refractory B-cell acute lymphoblastic leukemia with high bone marrow lymphoblast percentage Secondary: To estimate CR rate To estimate the minimimal residual disease (MRD) negativity rate in subjects achieving a CR or CRh To estimate 2-year relapse-free survival (RFS) To estimate 2-year overall survival (OS) To estimate ORR, CR, CRh, 2-year RFS, and 2-year OS in the Ph/BCR-ABL1-negative and Ph/BCR-ABL1–positive populations separately To determine the allogeneic hematopoietic cell transplantation rate in transplant-eligible subjects To determine the safety and tolerability of blinatumomab in combination with pembrolizumab Exploratory: To determine PD-1 expression on T-cells and PD-L1 and PD-L2 protein expression on lymphoblasts at diagnosis and in response to therapy To determine changes in bone marrow and peripheral blood T-cell populations in response to therapy with blinatumomab and the combination of blinatumomab and pembrolizumab. To determine changes in PD-1, PD-L1 and PD-L2 expression with blinatumomab exposure and correlation with disease response To determine changes in cytokine response with therapy and correlate with PD-1, PD-L1 and PD-L2 expression changes
Number of Subjects	24

Diagnosis and Main Inclusion Criteria	<u>Inclusion</u> 1. Relapsed or refractory CD19-positive B-lineage acute lymphoblastic leukemia having received at least 1 prior line of therapy 2. Philadelphia chromosome/BCR-ABL1-positive B-lineage ALL must have failed at least 1 second or third generation tyrosine kinase inhibitor (TKI) or be intolerant to TKIs 3. Greater than 50% lymphoblasts on screening bone marrow aspirate or biopsy 4. Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) from a sample obtained from the current relapse 5. Adults 18 years of age or older 6. ECOG performance status of 0 or 1 7. Adequate organ function defined as: - Bilirubin <1.5x upper limit of normal (ULN) unless believed due to leukemic infiltration - AST or ALT ≤2.5x ULN unless believed due to leukemic infiltration - creatinine clearance >60 mL/min/1.73 m2 unless reduced creatinine clearance felt by investigator to be acute and reversible 8. Ability to understand and the willingness to sign a written informed consent. 9. Women of child-bearing potential and men with partners of child-bearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. a. A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: i. Has not undergone a hysterectomy or bilateral oophorectomy; or ii. Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months) 10. Women of child-bearing potential has negative pregnancy test within 72 hours of initiating study drug dosing.

	11. Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential even if they had a successful vasectomy starting with the first dose of study therapy through 120 days after the last dose of study therapy. 12. Corticosteroids and hydroxyurea are permitted after screening bone marrow biopsy is performed and for up to 7 days prior to starting study therapy <u>Exclusion</u> 1. Allogeneic HSCT within 5 years of study drug administration 2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment. 3. GM-CSF or G-CSF use within 2 weeks of study treatment and throughout the study. 4. Prior checkpoint inhibitor therapy including anti-PD1, anti-PD-L1, anti-CTLA4, anti- CD137, or anti-PD-L2 therapy 5. Prior treatment with any CD19-directed therapy (e.g. blinatumomab, CD19-directed chimeric antigen receptor T-cell therapy, anti-CD19 antibodies). 6. Clinical evidence of active CNS involvement by leukemia 7. History of neurologic disorder including but not limitied to: prior seizure, epilepsy, structural brain abnormality, benign brain tumor, stroke, brain injuries, dementia, movement disorder or other significant CNS abnormalities. 8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in sito cervical cancer that has undergone potentially curative therapy. 9. Burkitt lymphoma/leukemia 10. Has a diagnosis of congenital immunodeficiency 11. Has a known history of active TB (Bacillus Tuberculosis) 12. Known HIV infection 13. Active hepatitis B or hepatitis C infection 14. Any uncontrolled infection 15. Has received a live vaccine within 30 days prior to first dose 16. Is pregnant or breastfeeding, or 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 trial treatment. 17. 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 Day 1 throughout the study period up to 120 days after the last dose of study therapy. 18. History of autoimmune disease 19. Known interstitial lung disease 20. Any evidence of active, non-infectious pneumonitis or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis 21. Patients who have received chemotherapy or radiotherapy within 4 weeks prior to entering the study or has not recovered from adverse events due to agents administered more than 4 weeks earlier. 22. Patients who are less than 4 weeks from surgery or have insufficient recovery from surgical-related trauma or wound healing. 23. History of allergic reactions attributed to compounds of similar chemical or biologic composition to blinatumomab or pembrolizumab or other agents used in study. 24. Known impaired cardiac function including any of the following: a) History or presence of clinically significant ventricular or atrial tachyarrhythmias; b) Clinically significant resting bradycardia (< 50 beats per minute); c) Myocardial infarction within 1 year of starting study drug; d) Other clinically significant heart disease (e.g., unstable angina, uncontrolled congestive heart failure, or uncontrolled hypertension). 25. Any condition that requires the use of corticosteroids after Day 1 of therapy with the exception of topical or inhaled steroids. Prednisone dose or equivalent of 5mg/day is allowed. 26. Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e., uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study

	requirements)
Study Product(s), Dose, Route, Regimen	Blinatumomab Pembrolizumab
Duration of administration	28 weeks
Reference therapy	Blinatumomab alone, historical (Topp et al. 2015)
Statistical Methodology	One-sided binomial, Kaplan Meier estimates, chi-squared

Period/ Procedure	**Screening**	**Treatment** (42 day cycles)																	
	-21 to -1	Cycle 1							Cycle 2				Cycle 3-5				End of Treatment	Follow up	Relapse
Day		1	8	14	15	28	29 +8	36	1	15	29 +8	36	1	15	29 +8[m]	36	Day 38 +8 days of Cycle 5	Every 3 Mos	
Informed Consent	X																		
Treatment																			
Pembrolizumab					X			X		X		X		X		X			
Blinatumomab		X[a]	X[b]						X[b]				X[b]						
Methotrexate	X[c]						X[c]				X[c]				X[c,m]		X		
Clinical Procedures																			
Review of Eligibility Criteria	X																		
Demographics	X																		
Medical History	X																		
Performance Status (ECOG)	X	X							X				X				X		
Vital Signs, Weight[d]	X	X							X				X				X	X	X
Height	X																		
Physical Exam[e]	X	X							X				X				X	X	X
PET/CT Scan (if palpable lymphadenopathy and/or evidence of extramedullary masses)[f]	X																X		X
CT Scan (if palpable lymphadenopathy and/or evidence of extramedullary masses)[f]							X				X								
Bone Marrow Aspiration/ Biopsy[g]	X			X			X				X				X[m]		X		X

Minimal Residual Disease[h]							X				X				X[m]		X		
Sample for FoundationOne Mutational Analysis [n]	X																		X
Statement of planned allogeneic HCT	X																		
Lumbar Puncture[i]	X						X				X				X[l]		X		X
CSF Studies[j]	X						X				X				X[l]		X		X
Day	Screening	1	8	14	15	28	29 +8	36	1	15	29+8	36	1	15	29+8 m	36	Day 38 +8 days of Cycle 5	Q3 MOs	Relapse
Laboratory Procedures																			
CBC with Differential	X	X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Metabolic Panel (CMP)[k]	X	X		X				X	X	X		X	X	X		X	X		X
Direct Bilirubin	X	X		X				X	X	X		X	X	X		X	X		X
Magnesium	X																		
Phosphate	X																		
Lactate Dehydrogenase	X																		
Uric Acid	X																		
Amylase	X			X				X	X	X		X	X	X		X	X		
Lipase	X			X				X	X	X		X	X	X		X	X		
Coagulation (INR, PT, PTT)	X																		
TSH, Free T4	X												X[l]						
Hepatitis B, C and HIV Serologies	X																		
Serum Pregnancy Test	X																		
Study Assessments																			
Adverse Events	X	X		X		X	X	X	X	X		X	X	X	X	X	X		

Concomitant Medications	X	X		X		X	X	X	X	X		X	X	X	X	X	X	X	X

a. Blinatumomab 9mcg/day CIV day 1-7
b. Blinatumomab 28mcg/day CIV
c. Methotrexate 15mg intrathecal at screening, day 29 +8 days of cycles 1-4, and day 38 +8 days of cycle 5
d. Vital signs (heart rate and oxygen saturation) to be monitored continuously and full vital signs (temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation) every 4 hours during at least the intial 72 hours of blinatumomab therapy, for 72 hours after all restart or step-up doses, and for at least the initial 72 hours following the first (Cycle 1, Day 15) and third (Cycle 2, Day 15) pembrolizumab doses.
e. Complete physical exam with full neurologic exam (section 6.1.6)
f. PET/CT with diagnostic CT chest/abdomen/pelvis (at screening, end of treatment and follow up) or CT chest/abdomen/pelvis if palpable lymphadenopathy or masses at diagnosis
g. Bone marrow aspirate and biopsy to include standard morphology, flow cytometry, karyotype, and in situ hybridization for t(9;22)(q34;q11.2)[BCR-ABL1]; t(v;11q23)[MLL rearranged]; t(12;21)(p13;q22)[ETV6-RUNX1]; t(1;19)(q23;p13.3)[TCF3-PBX1], institutional standard supercedes
h. Minimal residual disease by multiparameter flow cytometry per section 7.1.3.
i. For patients with screening WBC >10,000, LP may be held until WBC ≤10,000. Patient eligible if patient has no signs or symptoms of active CNS involvement at screening.
j. CSF studies with each lumbar puncture: Cell count with differential, cytology, flow cytometry
k. Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.
l. TSH and Free T4 to only be collected on Day 1 of Cycle 3 and 5
m. Only during cycles 3 and 4
n. See section 6.5.1.1 for details

FLOW CHART- Research Related Samples

Schedule of Events for Research Related Samples														
	Screening	Cycle 1												Cycle 2
Day		1	2	3	8	9	10	14	15	16	17	21	29 +8	Day 29 +8
PD-L1 and PD-L2 lymphoblast Western blotting[a]	X							X					X	
Bone Marrow Correlative Studies (PD-1, PD-L1 Testing), Peripheral blood T-cell subsets[b]	X							X					X	X
Serum Cytokine Assay[c]		X	X	X	X	X	X		X	X	X	X		

a. to be shipped to UCSD per section 6.5.1.2

b. bone marrow aspirate (5 mL) sent to Morris Lab, UCSD per section 6.5.1.3
c. to be drawn prior to, 24 (+/- 2 hours), 48 hours (+/- 2 hours), and 7 days after blinatumomab, blinatumomab dose increase, and first pembrolizumab dose, Sent to UCSD per section 6.5.1.4

1. BACKGROUND AND RATIONALE

1.1 Disease Background

1.1.1 Relapsed ALL

Despite improvements in initial therapy for newly diagnosed ALL, the majority of adult patients with newly-diagnosed ALL will ultimately relapse and die of their disease. Outcomes after relapse are very poor with few long-term survivors. Fielding et al. reported outcomes of 609 adult patients with acute lymphoblastic leukemia on the MRC UKALL12/ECOG 2993 study relapsing after complete remission. For the entire cohort, 5-year overall survival was 7% with younger age, late relapse, male sex, and extramedullary relapse excluding CNS relapse being favorable factors for survival. Excluding patients who had relapsed after prior hematopoietic cell transplantation (HCT), 5-year survival with chemotherapy alone was only 4% but for sibling allogeneic HCT, matched-unrelated donor HCT, and autologous HCT it was 23%, 16%, and 15%, respectively (Figure 1B)[1]. Attaining a complete remission is generally a precondition for high-dose therapy with HCT and more effective salvage therapy may improve CR rates and the proportion of relapsed patients who proceed to potentially curative allogeneic HCT.

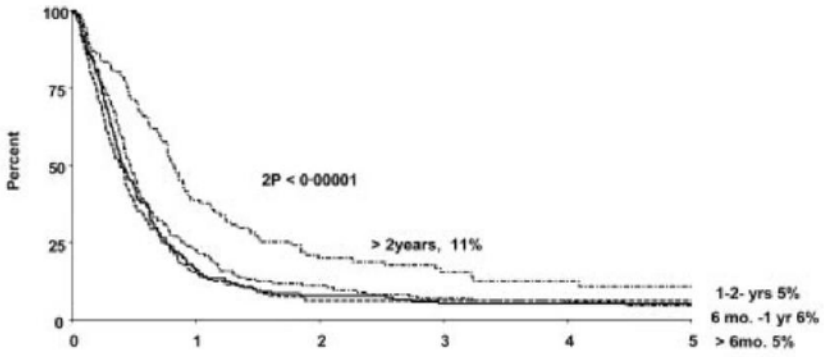


Figure 1A: Overall survival after relapse by time form CR to relapse.

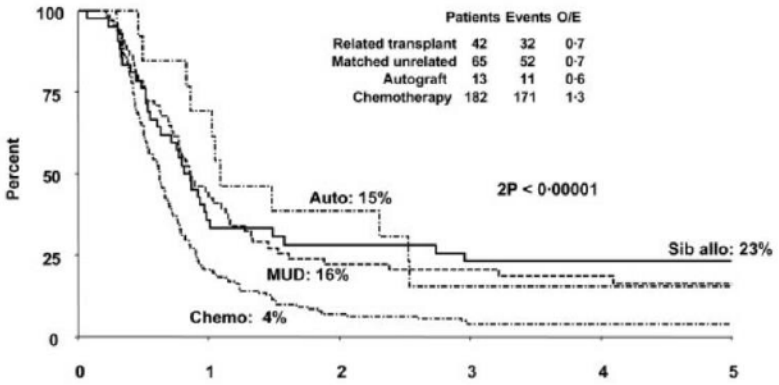


Figure 1B: Overall survival after relapse by post-relapse therapy in patients who had not previously undergone myeloablative HCT.

1.1.2 Treatment options for relapsed or refractory ALL

Treatment of relapsed ALL generally depends on the timing of relapse, disease lineage, prior allogeneic hematopoietic cell transplantation, patient age, and patient fitness for aggressive therapy. Until recently, traditional multi-agent chemotherapy for relapsed ALL was the only treatment option. For patients with late first relapse (generally CR1 duration > 2 years), re-treatment with the initial induction regimen can yield excellent results and is considered standard management even with the advent of targeted therapies. In patients with early relapse, traditional combination chemotherapy regimens employing high-dose cytarabine, high-dose methotrexate, or clofarabine can achieve CR rates of approximately 20-40% although patient selection for these therapies based on prior chemotherapy exposure and overall fitness is important to achieve these CR rates.

New formulations of existing drugs known to be active in ALL hold some promise to improve remission rates for relapsed or refractory ALL. Liposomal vincristine (Marquibo®) has been studied as monotherapy or in combination with dexamethasone for relapsed ALL. A Phase II study of liposomal vincristine 2.25 mg/m2 IV weekly in patients with relapsed or refractory ALL demonstrated a CR rate of 11% and on overall complete response rate (CR + CRi) of 20%. Median duration of CR/CRi was only 23 weeks. Survival was also short with a median overall survival of 4.6 months for all patients and 7.7 months for patients achieving a CR/CRi. Survival at 24 months was only 4% [2]. No randomized studies have been completed to show that the liposomal formulation of vincristine is superior to naked vincristine for either efficacy or safety. The low complete response rates with liposomal vincristine, short survival, unclear superiority to naked vincristine, and the unknown safety and efficacy of the drug in combination therapy has limited the use of this drug in relapsed or refractory ALL.

More recently, numerous targeted agents and approaches have been developed for B-lineage ALL. Inotuzumab-ozagamycin is an antibody-drug conjugated composed of a humanized monoclonal antibody targeting CD22 linked to anti-tumor antibiotic calicheamicin. After binding to the surface of CD22-positive cells including CD22-positive lymphoblasts, the inotuzumab-ozagamycin is internalized into lysosomes where the linker is cleaved releasing calicheamin which binds the minor groove of DNA and causes strand breakage. Kantarjian et al. reported ninety patients with relapsed or refractory CD22+ B-lineage ALL treated with one of two schedules on inotuzumab-ozagamycin. The CR rate was 19% with on overall response rate (CR + CRp + bone marrow CR) of 58% with no difference in response seen between single-dose and weekly-dose schedules but with improved tolerability with weekly dosing of drug. With the weekly schedule of inotuzumab-ozagamycin, rates of VOD/SOS after allogeneic hematopoietic cell transplantation were low at 7%. Despite excellent activity, median OS was only 6.2 months with all patients not undergoing allogeneic HCT dying within 20 months of starting therapy [3]. A Phase III study randomized 326 adults with relapsed or refractory B-cell ALL to weekly inotuzumab ozagamicin or investigator's-choice regimen (FLAG, high-dose cytarabine, or mitoxantrone/cytarabine). An early report of 218 patients evaluable for response showed a response benefit with inotuzumab ozagamicin. CR/CRi was 80.7% in all patients and 87.7% in first salvage patients treated with inotuzumab ozagamicin versus 33.3% and 31.3% in those treated with SOC regimens ($p<0.0001$). The median duration of remission was short at 4.6 months but superior to 3.1 months in the comparator arm ($p=0.02$). Patients are currently being followed for overall survival [19].

Engineering of autologous T-cells to express chimeric-antigen receptors (CARs) targeting CD19 on the surface of B-lineage lymphoblasts is a novel and powerful strategy currently in clinical trials. Patient T-cells are manipulated *in vitro* to express a chimeric T-cell receptor containing an

extracellular single-chain variable fragment (scFv) targeting CD19, a transmembrane domain, an intracellular costimulatory domain(s), and a signaling domain (e.g. CD3). The engineered cells are then reinfused into the patient where the cells expand and kill cells expressing CD19, including normal B-lymphocytes. Complete response rates in relapsed/refractory ALL are >80% with a potentially fatal cytokine release syndrome and persistent B-cell aplasia being concerning side effects [4,5].

1.2 Study Agent(s)

1.2.1 Blinatumomab

Blinatumomab is a bifunctional T-cell engaging (BiTE) antibody linking the variable domain of an anti-CD3 monoclonal antibody with the variable domain of an anti-CD19 monoclonal antibody. The configuration leads to an unstable bifunctional antibody with a short half-life and thus requires continuous IV infusion to be efficacious. The drug binds both the CD3 component of the T-cell receptor and CD19 on the surface of normal and malignant B-cells bringing cytotoxic T-cells into close proximity with CD19-positive cells. This engagement leads to T-cell activation with target cell lysis and concomitant T-cell proliferation. The vast majority of B-lineage ALL expresses CD19 on the cell surface.

Blinatumomab has been shown to be efficacious in the MRD+ B-lineage ALL and in relapsed/refractory B-lineage ALL. A small phase II study evaluated blinatumomab given by 4 week continuous intravenous infusion at a dose of 15 mcg/m2/24 hours in B-lineage ALL patients with persistent or recurrent minimal residual disease (MRD) after front-line therapy. Of 20 evaluable patients, 16 achieved MRD negativity for an MRD response rate of 80%. With short median follow-up of 273 days, responses appeared durable in the majority of patients [6]. In a subsequent report of the same study population with follow-up of 33 months, the hematologic relapse-free survival of the 20 patient cohort was 61% and only slightly better at 69% in 9 patients who underwent allogeneic HCT after MRD response to blinatumomab. For 6 Ph-negative ALL patients with MRD response to blinatumomab, 4 continued in hematologic and molecular complete remission. Findings suggested that blinatumomab could lead to prolonged remissions and potentially cures in patients with persistent or relapsed MRD [7].

A Phase 2, single-arm, multi-center study, blinatumomab was given at 9 µg/day for the first 7 days and 28 µg/day thereafter by continuous intravenous infusion over 4 weeks every 6 weeks for up to five cycles to 189 subjects with relapsed or refractory B-lineage ALL. Blinatumomab monotherapy yielded an overall response rate (CR + CRh) of 43% with all responses occurring within 2 cycles of therapy (Topp et al. 2015). However, blinatumomab achieves CR/CRh rates of only 29% in B-ALL patients with ≥50% lymphoblasts in the bone marrow versus 73% in subjects with <50% lymphoblasts in the bone marrow. Median overall survival was 6.7 months for all patients and 3.1 months for patient not achieving a CR/CRh [8].

Blinatumomab is generally well tolerated. Reversible neurotoxicity including confusion, aphasia, paresis, and seizures may occur with blinatumomab. A potentially serious but rare toxicity of blinatumomab is a cytokine release syndrome (CRS) characterized by fever, hypotension, and occasionally pulmonary toxicity leading to acute respiratory distress syndrome. The incidence of Grade ≥3 CRS in 211 patients studied was 1.3%. The physiologic consequences of the cytokine release syndrome are associated with elevated levels of proinflammatory cytokines including IFN-gamma, TNF-alpha, IL-10, IL-6, and IL-2 [9]. The syndrome is associated with high disease burden and can be ameliorated with corticosteroids or the anti-IL6 antibody tocilizumab [10].

The relatively high overall response rate with blinatumomab monotherapy led to FDA approval of the drug in 2015 and it is now a standard treatment option for relapsed or refractory B-cell ALL. Despite its impressive activity in patients with MRD+ and low bone marrow blast count ALL, response rates of approximately 30% in patients with bone marrow blasts counts greater than 50% parallel those seen with multiagent chemotherapy. The reasons for this disparity in response are unclear and insufficient T-cell activation by blinatumomab or suboptimal dosing of blinatumomab may be potential mechanisms.

1.2.2 Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) 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 seems to correlate with improved prognosis and long-term survival in many solid tumors.

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 is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM 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. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. 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. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein 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. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This 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. Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the

IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KeytrudaTM (pembrolizumab) has recently been approved in the United States for the treatment of patients with non-small cell lung cancer or those with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

PD-1 inhibitors including pembrolizumab have promising activity in solid tumors although their activity in acute leukemia is unknown. A Phase Ib/II study of pembrolizumab in relapsed/refractory hematologic malignancies is ongoing. PD-L1, but not PD-L2, is expressed in a subset of ALL primary cells and in most lymphoid leukemia/lymphoma cell lines [11,12]. PD-L1 also tends to be upregulated in the setting of relapsed malignancies including ALL [13,14]. IFN-gamma and TNF-alpha cause upregulation of PD-L1 in acute leukemia [15] which may potentially contribute to resistance to the effects of blinatumomab given the high expression of IFN-gamma, TNF-alpha and other inflammatory cytokines with blinatumomab treatment. Taken together, pembrolizumab holds promise to augment the effect of blinatumomab in patients with relapsed or refractory B-lineage ALL.

Pembrolizumab is generally well tolerated as monotherapy with principal adverse events being rare immune checkpoint blockade-related toxicities. Adverse events in 411 melanoma patients included pneumonitis in 2.9% (0.2% Grade 3), immune-mediated colitis in 1% (0.5% Grade 3), hepatitis in 0.5% (0.2% Grade 4), hypophysitis in 0.5% (0.2% Grade 4), hyperthyroidism in 1.2% (0.2% Grade 3), hypothyroidism in 8.3% (0.2 % Grade 3), type I diabetes mellitus, and immune-mediated nephritis in 0.7% (0.5% Grade 3 or 4). Treatment with prednisone 40 mg or greater per day led to resolution of symptoms in the large majority of patients. Infusion reactions are rare with pembrolizumab but may occur. The effect of pembrolizumab on the developing fetus is unknown.

Fixed dose pembrolizumab at 200 mg every 3 weeks is being used in this study based on results of KEYNOTE-001, a randomized study comparing pembrolizumab 2 mg/kg to 10 mg/kg IV every 3 weeks in patients with advanced melanoma. No differences were seen in efficacy or safety between the two dose levels. Overall response rates to pembrolizumab were 26% at the 2 mg/kg dose and 26% at the 10 mg/kg dose. Pharmacokinetic studies across tumor types failed to demonstrate differences in exposure based on tumor type or tumor burden. The equivalent efficacy and toxicity of pembrolizumab at 2 mg/kg relative to higher doses has led Merck to recommend fixed dosing of pembrolizumab at 200 mg IV every 3 weeks a dose that should maintain maximal clinical activity. PK studies in KEYNOTE-001 overlapping exposure between the 2 mg/kg and 200 mg doses with the 200 mg dose leading to slightly higher individual exposure [20]. As such, there is no expectation of significant differences in exposure relative to prior studies using the fixed 200 mg pembrolizumab dose in this study. .

1.3 Rationale for Combining Blinatumomab and Pembrolizumab

Mechanisms of resistance to blinatumomab are not well understood although inhibition of or suboptimal T-cell activation may play an important role. PD-L1 and PD-L2 expression and upregulation in lymphoblasts and the bone marrow microenvironment at baseline and in response to cytokines including those released upon blinatumomab exposure may inhibit T-cell function through the PD-1 receptor and lead to resistance to blinatumomab. A recent case report supports this hypothesis. A 32-year old patient with relapsed B-cell ALL with 30% blasts in the bone marrow was treated with blinatumomab and developed 4 days of fever at the start of therapy. Bone marrow biopsy at completion of one cycle blinatumomab showed 60%

lymphobalsts with homogeneous expression of CD19. Immunohistochemistry for PD-1 and PD-L1 and pre- and post-blinatumomab bone marrow samples showed a moderate increase in PD-1 expression in lymphocytes (5% vs 15%) but marked upregulation of PD-L1 on marrow lymphoblasts (2% vs. 40%). *In vitro*, the patient's T-cells were also less able to effect blinatumomab-mediated lymphoblast lysis relative to healthy donor T-cells [21]. We hypothesize that part of the resistance to therapy with blinatumomab is mediated by the exuberant cytokine release seen with higher disease burden leading to increased expression of PD-L1 and PD-L2. Enhancing T-cell activity through use of the PD-1 inhibitor pembrolizumab is predicted to augment the activity of blinatumomab and convert more patients to complete remission and prolong remission durations. This study will also act to expand knowledge of PD-L1 and PD-L2 dynamics in response to blinatumomab. It will also be a paradigm for the addition of checkpoint inhibitors to therapy with bifunctional T-cell engaging antibodies currently in development for targeting other liquid and solid tumors.

Blinatumomab is highly active in patients with low bone marrow lymphoblast count at relapse but has low overall response rates seen in relapsed/refractory B-lineage ALL patients with bone marrow blast count >50%. The level of response in high blast count ALL parallels that observed with traditional multiagent chemotherapy and improving response in this group of patients may improve survival and allow a greater proportion of blinatumomab treated patients to proceed to allogeneic HCT. Here we study this high-risk population and the ability of the PD-1 inhibitor pembrolizumab given in combination with blinatumomab to improve the blinatumomab CR/CRh rate.

1.4 Correlative Studies

1.4.1 PD-1, PD-L1 and PD-L2 expression and T-cell dynamics

Both PD-L1 and PD-L2 are ligands for PD-1 and inhibition of PD-1 disrupts interaction with both ligands leading to enhanced T-cell activation and cytolysis. PD-L1 is constitutively expressed on numerous types of non-immune and immune cells including dendritic cells, macrophages, and T-cells. In addition, PD-L1 is upregulated in response to inflammatory cytokines likely as a protective mechanism to prevent T-cell mediated killing of healthy cells. This mechanism, however, may confer resistance to immunotherapies such as blinatumomab. PD-L1 is expressed on the surface of the majority of acute lymphoblastic leukemia cells and in nearly all lymphoblastic leukemia model cell lines [12]. The expression pattern of PD-L2 is less well defined potentially as this inhibitory molecule is principally expressed in response to Th2 cytokines including IL-4, γ-chain cytokines, interferon-γ, and TNF-α. [16]. The goal of these correlative studies is to better define PD-1 expression on bone marrow T-cells and PD-L1 and PD-L2 in lymphoblasts and the bone marrow microenvironment and to correlate PD-L1 and PD-L2 expression with response to blinatumomab and the combination of blinatumomab with pembrolizumab. In addition, dynamic changes in T-cell populations in the marrow will be assessed by flow cytometry on marrow aspirates.

1.4.2 Cytokine studies

Cytokine release syndrome is the principal life-threatening event associated with blinatumomab exposure. In the MRD+ population, Klinger et al. showed the cytokine elevations including IL-2, IL-6, IL-10, TNF-α, and interferon-γ peak about 8-16 hours after starting blinatumomab and subsequently decrease reaching near baseline levels by 48 hours after the start of infusion [9]. More prolonged and severe cytokine elevation lasting days can occur in patients with a high disease burden leading to potentially fatal cytokine release syndrome [10]. Numerous cytokines including IL-2, IL-7, IL-15, IL-21, TNF-α, and interferon-γ are known to lead to upregulation of

PD-L1 and PD-L2 to help negative modulate immune responses. This process may have untoward effects in terms of treatment with immunotherapies such as blinatumomab where maximal T-cell activation in response to drug may be needed to eradicate disease. For this study, we plan to study the pattern of inflammatory cytokine release after blinatumomab alone and the combination of blinatumomab and pembrolizumab and to correlate cytokine release with changes in lymphoblast and bone marrow PD-L1 and PD-L2 expression.

2. STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To determine if the addition of pembrolizumab to blinatumomab improves the overall response rate (CR+ CRh) relative to blinatumomab alone in adult subjects with relapsed or refractory B-cell acute lymphoblastic leukemia with high bone marrow lymphoblast percentage

2.2 Secondary Objectives

2.2.1 To estimate CR rate

2.2.2 To estimate the minimimal residual disease (MRD) negativity rate in subjects achieving a CR or CRh

2.2.3 To estimate 2-year relapse-free survival

2.2.4 To estimate 2-year overall survival

2.2.5 To estimate ORR, CR, CRh, 2-year RFS, and 2-year OS in the Ph/BCR-ABL1-negative and Ph/BCR-ABL1–positive populations separately

2.2.6 To determine the allogeneic hematopoietic cell transplantation rate in transplant-eligible subjects

2.2.7 To determine the safety and tolerability of blinatumomab in combination with pembrolizumab

2.3 Exploratory Objectives

2.3.1 To determine PD-1 expression on T-cells and PD-L1 and PD-L2 protein expression on lymphoblasts at diagnosis and in response to therapy

2.3.2 To determine changes in bone marrow and peripheral blood T-cell populations in response to therapy with blinatumomab and the combination of blinatumomab and pembrolizumab.

2.3.3 To determine changes in PD-1, PD-L1 and PD-L2 expression with blinatumomab exposure and correlation with disease response.

2.3.4 To determine changes in cytokine response with therapy and correlate with PD-1, PD-L1 and PD-L2 expression changes

3. Study Endpoints

3.1 Primary Endpoint

3.1.1 Overall response rate (ORR) with the combination of blinatumomab and pembrolizumab in adult subjects with relapsed or refractory B-cell acute lymphoblastic leukemia be defined as the CR rate plus the CRh rate after 1 or 2 cycles of combination therapy. CR is defined as <5% lymphoblast in the bone marrow without evidence of circulating lymphoblasts or extramedullary disease. CRh is defined as for CR except with platelet count >50,000/microliter, hemoglobin >7 g/dL, and ANC >500/microliter. ORR will be compared to historical controls treated with blinatumomab alone.

3.2 Secondary Endpoints

3.2.1 CR rate as defined above.

3.2.2 Minimal residual disease (MRD) negativity in subjects achieving a CR or CRh will be defined as less than 0.01% residual lymphoblasts by multiparameter flow cytometry.

3.2.3 2-year relapse-free survival (RFS) will be defined as the time from achieving CR or CRh to relapse defined as the reappearance of lymphoblasts in bone marrow or blood at >5% of cells or reappearance of extramedullary disease.

3.2.4 2-year overall survival (OS) will be defined as the time from starting study therapy to death from any cause.

3.2.5 ORR, CR rate, 2-year RFS, and 2-year OS in the Ph/BCR-ABL1-negative and Ph/BCR-ABL1–positive populations separately.

3.2.6 Allogeneic hematopoietic cell transplantation (HCT) rate in transplant-eligible subjects will be defined as the number of patients eligible for allogeneic HCT as determined by the investigator who actually proceed to transplant.

3.2.7 Safety and tolerability of blinatumomab in combination with pembrolizumab will be defined by treatment-emergent Grade 2-5 adverse events (AEs) defined using NCI CTCAE v4.03 toxicity criteria attributable to study therapy.

3.3 Exploratory Endpoints

3.3.1 Changes in PD-1 protein expression on T-cells and PD-L1 and PD-L2 protein expression on marrow lymphoblasts will by assessed by flow cytometry and Western blotting.

3.3.2 Changes in bone marrow and peripheral blood T-cell populations by flow cytometry in response to therapy with blinatumomab and the combination of blinatumomab and pembrolizumab.

3.3.3 Levels of T-cell PD-1, and lymphoblast PD-L1 and PD-L2 expression by flow cytometry and Western blotting with study therapy will be correlated with disease response.

3.3.4 Changes in serum cytokines with therapy and correlation with PD-1, PD-L1 and PD-L2 protein expression changes

4. PATIENT ELIGIBILITY

4.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study.

4.1.1 Relapsed or refractory CD19-positive B-lineage acute lymphoblastic leukemia having received at least 1 prior line of therapy

4.1.2 Philadelphia chromosome/BCR-ABL1-positive B-lineage ALL must have failed at least 1 second or third generation tyrosine kinase inhibitor (TKI) or be intolerant to TKIs

4.1.3 Greater than 50% lymphoblasts on screening bone marrow aspirate or biopsy

4.1.4 Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) from a sample obtained from the current relapse

4.1.5 Adults 18 years of age or older

4.1.6 ECOG performance status of 0 or 1

4.1.7 Adequate organ function defined as:

-bilirubin <1.5x upper limit of normal (ULN) unless believed due to leukemic infiltration
-AST or ALT ≤2.5x ULN unless believed due to leukemic infiltration
-creatinine clearance ≥60 mL/min/1.73 m^2 unless reduced creatinine clearance felt by investigator to be acute and reversible
-absence of unstable cardiac disease defined as myocardial infarction with 6 months, uncontrolled heart failure, or uncontrolled cardiac arrythmia

4.1.8 Ability to understand and the willingness to sign a written informed consent.

4.1.9 Women of child-bearing potential and men with partners of child-bearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

- A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
  - Has not undergone a hysterectomy or bilateral oophorectomy; or
  - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)

4.1.10 Women of child-bearing potential has negative pregnancy test within 72 hours of initiating study drug dosing.

4.1.11 Male subjects must agree to use a latex condom during sexual contact with females of childbearing potential even if they have had a successful vasectomy starting with the first dose of study therapy through 120 days after the last dose of study therapy.

4.1.12 Corticosteroids and hydroxyurea are permitted after screening bone marrow biopsy is performed and for up to 7 days prior to starting study therapy

4.2 Exclusion Criteria

Subjects meeting any of the exclusion criteria at baseline will be excluded from study participation.

4.2.1 Allogeneic hematopoietic cell transplantation within 5 years of study drug administration

4.2.2 Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

4.2.3 GM-CSF or G-CSF use within 2 weeks of study treatment and throughout the study

4.2.4 Prior checkpoint inhibitor therapy including anti-PD1, anti-PD-L1, anti-CTLA4, anti-CD137, or anti-PD-L2 therapy

4.2.5 Prior treatment with any CD19-directed therapy (e.g. blinatumomab, CD19-directed chimeric antigen receptor T-cell therapy, anti-CD19 antibodies).

4.2.6 Clinical evidence of active CNS or testicular involvement by leukemia as documented by signs and symptoms on physical exam and/or positive LP.

–Active CNS disease by signs and symtpoms or active CNS_2/3 disease by cell counts and cytology. History of neurologic disorder including but not limitied to: prior seizure, epilepsy, structural brain abnormality, benign brain tumor, stroke, brain injuries, dementia, movement disorder or other significant CNS abnormalities.

4.2.7 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

4.2.8 Burkitt lymphoma/leukemia

4.2.9 Has a diagnosis of congenital immunodeficiency

4.2.10 Has a known history of active TB (Bacillus Tuberculosis)

4.2.11 Known HIV infection

4.2.12 Active hepatitis B or hepatitis C infection

4.2.13 Any uncontrolled infection

4.2.14 Has received a live vaccine within 30 days prior to first dose

4.2.15 Is pregnant or breastfeeding, or 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 trial treatment.

4.2.16 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 Day 1 throughout the study period up to 120 days after the last dose of study therapy.

4.2.17 History of autoimmune disease

4.2.18 Known interstitial lung disease

4.2.19 Any evidence of active, non-infectious pneumonitis or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

4.2.20 Patients who have received chemotherapy or radiotherapy within 2 weeks prior to entering the study or has not recovered from adverse events due to agents administered more than 2 weeks earlier.

4.2.21 Patients who are less than 4 weeks from surgery or have insufficient recovery from surgical-related trauma or wound healing.

4.2.22 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Blinatumomab or Pembrolizumab or other agents used in study.

4.2.23 Known impaired cardiac function including any of the following:

- History or presence of clinically significant ventricular or atrial tachyarrhythmias;
- Clinically significant resting bradycardia (< 50 beats per minute);
- Myocardial infarction within 1 year of starting study drug;
- Other clinically significant heart disease (e.g., unstable angina, congestive heart failure, or uncontrolled hypertension).

4.2.24 Any condition that requires the use of corticosteroids outside of corticosteroids defined in the protocol after Day 1 of therapy with the exception of topical or inhaled steroids

4.2.25 Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e., uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements.

5. TREATMENT PLAN

5.1 Treatment dosage and administration

5.1.1 Treatment summary

The study will be conducted in 2 stages:

Stage 1 is to ensure safety of pembrolizumab in combination with blinatumomab.

Dose Limiting Toxicity (DLT) is defined as a clinically significant adverse event that is considered by the investigator to be probably or definitely related to pembrolizumab or the combination of pembrolizumab and blinatumomab occurring within 42 days of the first dose of pembrolizumab on Day 15 of Cycle 1 as follows:

- Any Grade 3-5 non-hematologic toxicity EXCEPT:
  - Grade 3 cytokine release syndrome that resolves in 7 days or less
  - Grade 3 neurotoxicity that resolves in 7 days or less
  - Grade 3 infections
  - Grade 3 or 4 febrile neutropenia unless deemed by investigator to be definitely related to pembrolizumab
  - Grade 3 or 4 laboratory abnormalities unless they warrant temporary discontinuation of pembrolizumab or permanent discontinuation of blinatumomab (see tables, 5.7.1 and 5.7.2)
  - Grade 3 or 4 lymphopenia
- Any clinically significant toxicity that precludes administration of the next scheduled dose for more than 14 days

If no DLTs are experienced in the first 3 subjects then enrollment will advance Stage 2. If 1 DLT is noted in the first 3 subjects then 3 additional subjects will be enrolled. If no further DLTs are noted in the additional 3 subjects then enrollment will proceed to Stage 2. If 2 or more DLTs are noted at the proposed pembrolizumab dose level and schedule then enrollment will be placed on hold and a dose reduction or schedule change will be considered after discussion of investigators.

The DLT monitoring period will be 42 days starting on Day 15 of Cycle 1. Subjects withdrawing from investigational treatment during the DLT monitoring period for a reason that is definitely unrelated to toxicity of the study agent (e.g. disease progression, patient withdrawl of consent) will be deemed not evaluable for DLT determination and will be replaced. All subjects in Stage 1 will need to complete the DLT monitoring period prior to proceeding with Stage 2.

Stage 2 of the study will include an expansion cohort of up to 21 additional subjects (for a total of 24 subjects) to evaluate the efficacy of the combination of blinatumomab and pembrolizumab.

5.1.2 Other therapeutic agents

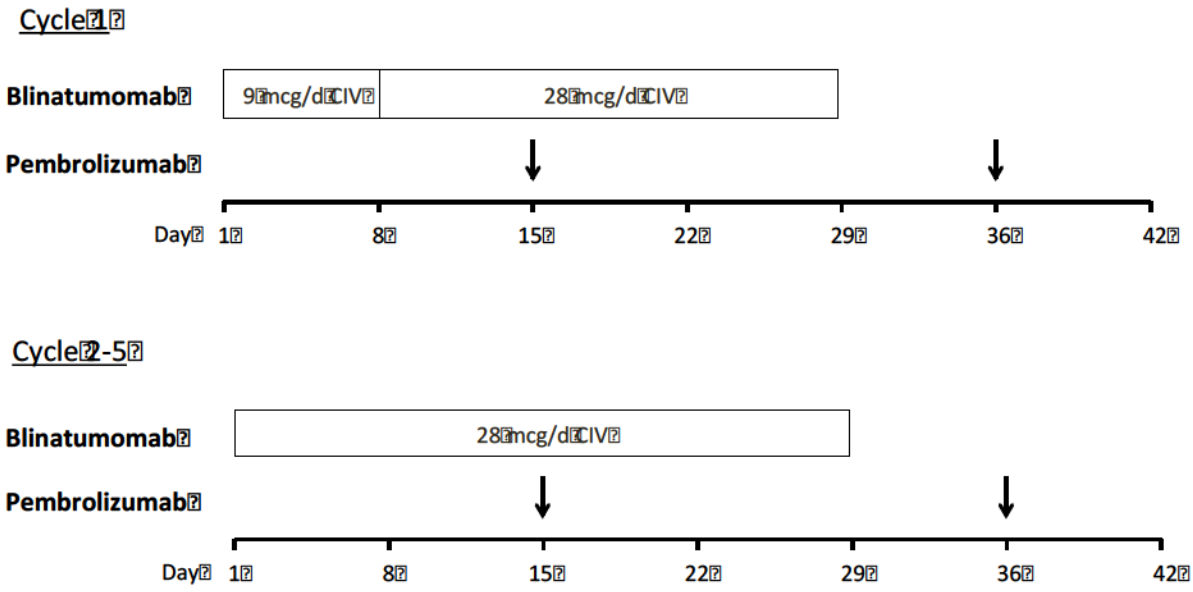
The use of therapeutic agents or approaches for malignancy outside of what is expressly stated in this protocol is strictly forbidden. This includes any study undefined use of the study specific therapeutic agents, the same class of agents, or agents not expressly defined in the protocol

with potential or known anti-leukemic activity. Institutional standard of care supportive medications are allowed as long as they do not have known or predicted anti-leukemic activity or are in conflict with study dictated supportive care.

5.1.3 Therapy

Both Stage 1 (safety lead-in) and Stage 2 (dose expansion) of this study will use the same regimen as detailed below.

Schema:



REGIMEN DESCRIPTION					
CYCLE 1					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Blinatumomab	Dexamethasone 20 mg IV once 1 hour (+/- 30 min) before start of infusion and 1 hour (+/- 30 min) prior to step-up dose on Day 8.	Day 1-7: 9 mcg/day Day 8-28: 28 mcg/day	Continuous IV infusion for 28 days. Bag changes every, 24 hours, 48 hours or 7 days (as appropriate).	Day 1-7 Day 8-28	6 weeks (42 days)
Pembrolizumab	None required, per institutional	200 mg	IV over 30 minutes	Days 15 and 36	

	standard of care				
Methotrexate	None required, per institutional standard of care	15 mg	Intrathecal or intraventircular	Day 29 + 8 days	
CYCLES 2–5					
Blinatumomab	Dexamethasone 20 mg IV once 1 hour (+/- 30 min) before start of infusion.	28 mcg/day	Continuous IV infusion for 28 days. Bag changes every 24hours, 48 hours or 7 days (as appropriate).	Days 1-28	6 weeks (42 days)
Pembrolizumab	None required, per institutional standard of care	200 mg	IV over 30 minutes	Days 15 and 36	
Methotrexate	None required, per institutional standard of care	15 mg	Intrathecal or intraventircular	Day 29 + 8 days	

See **Section 9.1** for details on administration of blinatumomab

Hospitalization requirements:

Cycle 1:
Hospital admission required from day 1 through day 18 and for at least 72 hours after pembrolizumab dose.

Cycle 2:
Hospital admission required day 1-3 for blinatumomab and for at least 72 hours after start of blinatumomab infusion.

Cycles 3-5:
Hospital admission required day 1-3 for blinatumomab and for at least 72 hours after start of blinatumomab infusion.

Hospital admission also required for any blinatumomab restart or step-dose increase and for 72 hours after restart or step-up dose.

Vital signs (heart rate and oxygen saturation) to be monitored continuously and full vital signs (temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation) every 4 hours

during at least the initial 72 hours of blinatumomab therapy, for 72 hours after all restart or step-up doses, and for at least the initial 72 hours following the first (Cycle 1, Day 15) pembrolizumab doses.

CNS Prophylaxis:

Methotrexate 15mg intrathecal or intraventricular at screening, day 29 + 8 days of cycle 1-4, and day 38 +8 days of cycle 5 (end of treatment)

Patients achieving a CR/CRh after 2 cycles will complete a total of 5 cycles of blinatumomab and pembrolizumab in the absence of relapse.

Patients not achieving a CR/CRh after 2 cycles of therapy or progressing after Day 15 of Cycle 1 will go off study.

Patients may proceed to allogeneic hematopoietic cell transplantation as consolidation any time after complete remission. Such patients will be censored for survival at time of initiation of conditioning regimen.

5.1.4 Stage I – Dose limiting toxicity definition and stopping rules

To determine the safety of pembrolizumab in combination with blinatumomab in patients with acute lymphoblastic leukemia, the combination will be administered to 3-6 patients with relapsed or refractory B-lineage acute lymphoblastic leukemia.

Toxicity will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. Adverse events will be assessed continuously throughout therapy.

Dose Limiting Toxicity (DLT) is defined as a clinically significant adverse event that is considered by the investigator to be probably or definitely related to pembrolizumab or the combination of pembrolizumab and blinatumomab occurring within 42 days of the first dose of pembrolizumab on Day 15 of Cycle 1 as follows:

- Any Grade 3-5 non-hematologic toxicity EXCEPT:
  - Grade 3 cytokine release syndrome that resolves in 7 days or less
  - Grade 3 neurotoxicity that resolves in 7 days or less
  - Grade 3 infections
  - Grade 3 or 4 febrile neutropenia unless deemed by investigator to be definitely related to pembrolizumab
  - Grade 3 or 4 laboratory abnormalities unless they warrant temporary discontinuation of pembrolizumab or permanent discontinuation of blinatumomab (see tables, 5.7.1 and 5.7.2)
  - Grade 3 or 4 lymphopenia
- Any clinically significant toxicity that precludes administration of the next scheduled dose for more than 14 days

Decision to proceed to Stage 2 of the study will be made as follows below.

Number of Patients with DLT	Decision Rule
0 out of 3	Proceed to Stage 2 of study.
1 out of 3	Enter at least 3 more patients. • If 0 of these 3 patients experience DLT, proceed to Stage 2 of study • If 1 or more of this group suffer DLT, then study will be placed on hold. Decision regarding dosing of pembrolizumab and continuation of study will be made after discussion between sponsors and investigators.
≥2	Study will be placed on hold and the FDA notified. Decision regarding dosing of pembrolizumab and continuation of study will be made after discussion between sponsors,investigators and FDA.
≤1 out of 6	Proceed to Stage 2 of study.

Subjects withdrawing from investigational treatment during the DLT monitoring period for a reason that is definitely unrelated to toxicity of the study agent (e.g. disease progression, patient withdrawal of consent) will be replaced.

5.1.5 Stage 2 - Dose expansion

If Stage 1 of the study proves safe, 18-21 additional subjects for a total of 24 subjects will be enrolled to assess the primary endpoint. Subjects from both stages will be included in the efficacy analysis.

5.1.6 Response assessment

Response will be assessed by bone marrow aspiration and biopsy on:

Cycle 1, Day 12, 13, or 14
Cycle 1, Day 29 + 8 days
Cycle 2, Day 29 + 8 days
Cycle 3, Day 29 + 8 days
Cycle 4, Day 29 + 8 days
Cycle 5, Day 38 + 8 days

Bone marrow aspiration and biopsy should occur at the time of any relapse or suspected relapse.

Bone marrow aspirates and biopsies should be sent for standard morphology, flow cytometry, karyotype, and *in situ* hybridization for any abnormalities documented on screening bone marrow studies.

Minimal residual disease testing on a first pull bone marrow aspirate should be sent overnight to University of Washington for analysis.

Requisition form is available in **Appendix C.** .

For patients with extramedullary disease at diagnosis, repeat imaging using the same modality as at diagnosis is to be performed to assess response on:

Cycle 1, Day 12, 13, or 14
Cycle 1, Day 29 + 8 days
Cycle 2, Day 29 + 8 days

Cycle 5, Day 38 + 8 days

Repeat imaging should occur at the time of any relapse or suspected relapse.

5.2 Pre-Medications

Pembrolizumab premedications:

No premedications are required although allowed at investigator discretion or institutional standard of care. Corticosteroids are not be used as premedications in the absence of prior infusion-related toxicity. For prior infusion-related reactions, administration of premedications should occur per institutional standard of care.

Blinatumomab premedications:

Dexamethasone 20 mg IV once one hour (+/- 30 min) prior to start of blinatumomab infusion on Day 1 of each cycle and one hour (+/- 30 min) prior to any dose increase from 9 mcg/day to 28 mcg/day.

In addition, if blinatumomab infusion is interrupted for more than 4 hours, dexamethasone 20 mg IV once one hour (+/- 30 min) prior to restarting blinatumomab should be given.

Other non-corticosteroid premedications may be administered per institutional standard of care.

5.3 Concomitant therapy

5.3.1 CNS relapse prophylaxis

Intrathecal chemotherapy to prevent CNS relapse will be administered as follows:

Methotrexate 15 mg intrathecal or intraventricular at screening, Day 29 + 8 days of cycles 1-4, and Days 38 + 8 days of cycle 5 (end of treatment).

5.3.2 Infection prophylaxis

5.3.2.1 Viral prophylaxis

Viral prophylaxis will consist of **acyclovir** to prevent HSV and VZV reactivation. Dosing as follows:

Acyclovir 400 or 800 mg oral twice daily continuously until completion of study therapy or longer at discretion of investigator

For patients undergoing treatment or prophylaxis with alternate antiviral agents targeting HSV and VZV, acyclovir prophylaxis may be suspended until completion of alternate therapy.

5.3.2.2 *Pneumocystis jiroveci* prophylaxis

All study patients receiving study therapy must receive *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis during active therapy per institutional standard of care. **Trimethoprim-sulfamethoxazole (TMP-SMX)** prophylaxis is recommended. Alternate PJP prophylaxis agents for patients intolerant of TMP-SMX include **dapsone, atovaquone,** or **pentamidine**.

5.3.2.3 Fungal prophylaxis

During periods of neutropenia patients should receive fungal prophylaxis. Recommended treatment is:

Fluconazole 400 mg oral daily for absolute neutrophil count <500/mcl

Alternate prophylactic regimens including no prophylaxis are allowed per local standard of care and investigator discretion.

5.3.2.4 Neutropenia prophylaxis

Prophylaxis during neutropenia including antibacterial and antifungal therapies is to be administered per local standard of care.

5.3.3 Other anti-leukemic therapies

No other anti-leukemic therapies outside of those described in this protocol are allowed.

5.3.4 Vaccines

Live vaccines within 30 days of treatment administration are prohibited.

5.3.5 Other concomitant medications

Medications required to treat adverse events, manage leukemia-related or treatment-related symptoms, maintain concurrent stable disease (e.g., controlled hypertension) as well as supportive care agents such as blood component transfusions, and pain medications are allowed per institutional standards of care and investigator discretion. The patient needs to notify the local investigational team about any new medications he/she takes after the start of the study medication. All medications other than study drug and significant non-drug therapies administered after the patient starts treatment with study drug must be recorded in the patient's medical record. Palliative and supportive care for disease-related symptoms, including pain medications, is permitted per local standards of care.

5.4 Prohibited concomitant therapy

Except as described in the protocol, **corticosteroids** are prohibited for any indication given the anti-leukemic activity of these agents interfering with interpretation of the study results. **Corticosteroids** are permitted to prevent or treat infusion reactions and cytokine release syndrome or Events of Clinical Interest (ECI, See appendix G). Topical or inhaled steroids are

permitted.

Use of **G-CSF** or **GM-CSF** is prohibited.

Any other potentially anti-neoplastic therapy is prohibited regardless of indication for administration.

Any biologic, antibody, or immunomodulatory agent, except as described in the protocol, is prohibited.

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be removed from the study.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. The use of alternative or complementary herbal or other dietary modifications should be discouraged.

5.5.2 Contraception

Pembrolizumab and blinatumomab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab or blinatumomab has 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 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods must be two barrier methods OR a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Day 1 throughout the study period and for 120 days after the last dose of study therapy.

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 defined in **Section 8.7**-Reporting of Pregnancy and Lactation to the Sponsor and to Merck and/or Amgen depending of exposure to pembrolizumab or blinatumomab or both. 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.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab or blinatumomab, the subject will immediately be removed from the study. 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 Sponsor and to Merck and/or Amgen depending on exposure to pembrolizumab or blinatumomab, respectively, without delay and within 24 hours to the Sponsor and within 2 working days to Merck and/or Amgen if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

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. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and to Merck and/or Amgen and followed as described above and in **Section 8.7**.

5.5.4 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.

5.6 Supportive Care Guidelines

In addition to the supportive care measures outlined above, 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 and in greater detail in the ECI guidance document. 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. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to **Section 5.7** below for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

5.7 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient

will be assessed for the development of toxicity except cytokine release syndrome (see below, grading/management per Lee et al. Blood 2014) according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity. As Blinatumomab is an approved treatment for this indication, reducing or withholding pembrolizumab should be considered as the first option in response to a toxicity prior to adjusting the Blinatumomab dosing.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab and blinatumomab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Tables below. See Section 5.6.1 in Events of Clinical Interest Guidance Document for additional supportive care guidelines.

All dose adjustments presume that the toxicity is determined by the investigator to be possibly, probably, or definitely related to blinatumomab, pembrolizumab, or both. Withholding the dose and dose adjustments should not occur if toxicity is felt unlikely to be or definitely not related to study blinatumomab, pembrolizumab, or both.

5.7.1 Management of non-Hematologic Toxicities

As Blinatumomab is an approved treatment for this indication, reducing or withholding pembrolizumab should be considered as the first option in response to a toxicity prior to adjusting the Blinatumomab dosing.

Any Grade 3 or severe AE that recurs should lead to permanent discontinuation of pembrolizumab, as should any persistent grade 2 or 3 AE (excluding endocrinopathies) that do not recover to grade 1 within 12 weeks of the last dose of pembrolizumab.

Cytokine Release Syndrome	Management for Blinatumomab	Management for Pembrolizumab
Grade 1 -Fever -Constitutional symtpoms	Continue infusion. Vigilant supportive care. Assess for infection.	No change in dose. Patient should be admitted for subsequent pembrolizumab dose given in combination with blinatumomab and monitored for at least 72 hours after pembrolizumab administration.
Grade 2 -Hypotension responsive to fluids or one low dose pressor** -Hypoxia: reponds to <40% O_2 -Organ toxicity: Grade 2	Continue infusion. Vigilant supportive care. Assess for infection.	No change in dose. Patient should be admitted for subsequent pembrolizumab dose given in combination with blinatumomab and monitored for at least 72 hours after pembrolizumab administration.
Grade 3 -Hypotension requiring multiple pressors or high dose pressors** -Hypoxia requiring ≥40% O_2	Withhold* until resolved then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids

Cytokine Release Syndrome	Management for Blinatumomab	Management for Pembrolizumab
-Organ toxicity: Grade 3 or Grade 4 transaminitis	Vigilant supportive care. Assess for infection. Consider administration of corticosteroids and/or tocilizumab.	Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Vasopressors Corticosteroids Tocilizumab 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. **Subject is permanently discontinued from further trial treatment administration.**
Grade 4 -Mechanical ventilation -Organ toxicity: Grade 4 excluding transaminitis	Off protocol therapy. Vigilant supportive care. Assess for infection. Consider administration of corticosteroids and/or tocilizumab..	Off protocol therapy. Vigilant supportive care. Assess for infection. Consider administration of corticosteroids and/or tocilizumab..
*Patients requiring a delay of blinatumomab >14 days should go off protocol therapy. **High-dose pressors include the following administered for ≥3 hours: norepinephrine ≥20 mcg/min, dopamine ≥10 mcg/kg/min, phenylephrine ≥200 mcg/min, epinephrine ≥10 mcg/min, if on vasopressin: vasopressin + norepinephrine equivalent of ≥10 mcg/min, if on combination of vasopressors: norepinephrine equivalent ≥20 mcg/min. NOREPINEPHRINE EQUIVALENT DOSE = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min)/2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min)/10]/		

Neurologic Toxicity	Management for Blinatumomab	Management for Pembrolizumab
Grade 1 or 2	Continue infusion.	No change in dose.
Grade 3	Withhold* until < Grade 2 for 3 days then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day or takes more than 7 days to improve to <Grade 2 then patient goes off protocol therapy.	Withhold* until < Grade 2 then resume at same dose. Missed doses should be given as close to missed scheduled dose as possible. Subsequent doses are given every 3 weeks.
Grade 4	Off protocol therapy	Off protocol therapy
Seizure, Grade 1 or 2	Withhold* until resolved and institute anticonvulsant prophylaxis (neurology consultation	Withhold until resolved then resume at same dose. Missed doses should be given as close to

Neurologic Toxicity	Management for Blinatumomab	Management for Pembrolizumab
	recommended) then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur.	missed scheduled dose as possible. Subsequent doses are given every 3 weeks until completion of planned cycles of therapy.
Seizure, Grade 3 or 4 or recurrent Grade 1 or 2	Off protocol therapy.	Off protocol therapy.
*Patients requiring a delay of blinatumomab >14 days should go off protocol therapy.		

Infusion Reactions	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	Refer to CRS section above.	Increase monitoring of vital signs as needed until clinical stability confirmed. No change in dose.
Grade 2	Refer to CRS section above.	Stop Infusion and monitor symptoms. 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. Withhold until ≤ Grade 1. Premedicate subsequent administration with hydrocortisone 100 mg IV once, diphenhydramine 50 mg IV or per oral (or equivalent alternate antihistamine), Tylenol 650 mg per oral. Subjects who develop Grade 2 toxicity despite adequate premedication permanently discontinue pembrolizumab.

Grade 3	Refer to CRS section above.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 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. **Subject is permanently discontinued from further trial treatment administration.**
Grade 4	Refer to CRS section above.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 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. **Subject is permanently discontinued from further trial treatment administration.**
*Patients requiring a delay of blinatumomab >14 days due to toxicity should go off protocol therapy. Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Pneumonitis	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose.
Grade 2	No change in dose.	Withhold pembrolizumab. Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. If pneumonitis recurs at Grade 2 or higher despite corticosteroids then permanently discontinue pembrolizumab. Restart when ≤ Grade 1. Missed doses are not made up.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If pneumonitis recurs then permanently discontinue blinatumomab.	Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Administer additional anti-inflammatory measures, as needed. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration. Discontinue pembrolizumab permanently.
Grade 4	Permanently discontinue blinatumomab.	Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Administer additional anti-inflammatory measures, as needed. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration. Discontinue pembrolizumab permanently.
*Patients requiring a delay of blinatumomab >14 days due to toxicity should go off protocol therapy.		

Diarrhea/Colitis	Management for Blinatumomab	Management for Pembrolizumab
General Management: All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Anti-motility agents may be administered per institutional standard of care. For Grade 2 or higher diarrhea/colitis thought related to study drug(s), gastroenterology consultation for colonoscopic evaluation with biopsies recommended to guide treatment.		
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	Withhold pembrolizumab. Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Restart pembrolizumab when ≤ Grade 1. Missed doses are not made up.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If diarrhea/colitis recurs then permanently discontinue blinatumomab.	Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Withhold pembrolizumab until ≤ Grade 1. Missed doses are not made up. If colitis recurs at Grade 3 or higher despite corticosteroids permanently discontinue pembrolizumab. If Grade 3 lasting >1 week despite oral prednisone, administer IV corticosteroids followed by high-dose oral corticosteroids per institutional standard. Permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. If Grade 3 lasting >1 week despite oral prednisone, administer IV corticosteroids followed by high-dose oral corticosteroids per institutional standard. Permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab >14 days due to toxicity should go off protocol therapy.		

Nephritis	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose.
Grade 2	No change in dose	Withhold until ≤ Grade 1. Missed doses are not made up. Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. If nephritis recurs at Grade 2 or higher despite corticosteroids then permanently discontinue pembrolizumab.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If nephritis recurs then permanently discontinue blinatumomab.	Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab > 14 days due to toxicity should go off protocol therapy.		

Hypophysitis	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose.
Grade 2	No change in dose	Withhold until ≤ Grade 1. Missed doses are not made up. Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Replacement of appropriate hormones may be required as the steroid dose is tapered. If hypophysitis recurs at Grade 2 or higher despite corticosteroids then permanently discontinue pembrolizumab.
Grade 3	Withhold* until resolved to ≤ Grade	Give methylprednisolone 2 mg/kg

Hypophysitis	Management for Blinatumomab	Management for Pembrolizumab
	1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If hypophysitis recurs then permanently discontinue blinatumomab.	IV once then prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Replacement of appropriate hormones may be required as the steroid dose is tapered. Permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Give methylprednisolone 2 mg/kg IV once then prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Replacement of appropriate hormones may be required as the steroid dose is tapered. Permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab >14 days due to toxicity should go off protocol therapy.		

Immune-mediated hepatitis	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose.
Grade 2	No change in dose	Withhold until ≤ Grade 1. Missed doses are not made up. Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. If immune-mediated hepatitis recurs at Grade 2 or higher despite corticosteroids then permanently discontinue pembrolizumab.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If immune-mediated hepatitis recurs then permanently discontinue blinatumomab.	Give methylprednisolone 2 mg/kg IV once then prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Replacement of appropriate hormones may be required as the steroid dose is

Immune-mediated hepatitis	Management for Blinatumomab	Management for Pembrolizumab
		tapered. Permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Give methylprednisolone 2 mg/kg IV once then prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Replacement of appropriate hormones may be required as the steroid dose is tapered. Permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab > 14 days due to toxicity should go off protocol therapy.		

Type I Diabetes Mellitus Developing on Pembrolizumab	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose.
Grade 2	No change in dose	No change in dose.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If type I diabetes mellitus recurs then permanently discontinue blinatumomab.	Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide. Permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.

Type I Diabetes Mellitus Developing on Pembrolizumab	Management for Blinatumomab	Management for Pembrolizumab
		Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide. Permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab > 14 days due to toxicity should go off protocol therapy.		

Immune-mediated hyperthyroidism	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose Treat with non-selective beta-blockers (eg. Propranolol) and/or thionamides as appropriate Monitor for sings and symptoms of the disorders
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If immune-mediated hyperthroidism recurs then permanently discontinue blinatumomab.	Withold of permanently discontinue pembrolizumab Treat with non-selective beta-blockers (eg. Propranolol) and/or thionamides as appropriate Monitor for sings and symptoms of the disorders
Grade 4	Permanently discontinue blinatumomab.	Withold of permanently discontinue pembrolizumab Treat with non-selective beta-blockers (eg. Propranolol) and/or thionamides as appropriate Monitor for sings and symptoms of the disorders
*Patients requiring a delay of blinatumomab > 14 days due to toxicity should go off protocol therapy.		

Immune-mediated hypothyroidism	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No Change in dose Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care Monitor for signs and symptoms of thyroid disorders.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If immune-mediate hypothyroidism recurs then permanently discontinue blinatumomab.	No change in dose Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care Monitor for signs and symptoms of thyroid disorders.
Grade 4	Permanently discontinue blinatumomab.	No change in dose Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care Monitor for signs and symptoms of thyroid disorders.
*Patients requiring a delay of blinatumomab > 14 days due to toxicity should go off protocol therapy.		

Other Immune-mediated Adverse Reactions	Management for Blinatumomab	Management for Pembrolizumab
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	Withhold until ≤ Grade 1. Missed doses are not made up. Start prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. If immune-mediated reaction recurs at Grade 2 or higher despite corticosteroids then permanently discontinue pembrolizumab.
Grade 3	Withhold* until resolved to ≤ Grade 1 then resume blinatumomab at 9	Give methylprednisolone 2 mg/kg IV once then prednisone 1-2

Other Immune-mediated Adverse Reactions	Management for Blinatumomab	Management for Pembrolizumab
	mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If immune-mediate reaction recurs then permanently discontinue blinatumomab.	mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Give methylprednisolone 2 mg/kg IV once then prednisone 1-2 mg/kg oral daily with taper over at least 4 weeks after resolution to ≤ Grade 1. Permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab > 14 days due to toxicity should go off protocol therapy.		

Other Non-Hematologic Adverse Reactions Despite Optimal Supportive Care	Management for Blinatumomab	Management for Pembrolizumab
Grade 1 or 2	Continue infusion.	No change in dose
Grade 3	Withhold* until < Grade 2 then resume blinatumomab at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If Grade 3 toxicity recurs despite optimal supportive care, permanently discontinue blinatumomab.	Withhold* until < Grade 2 then resume at same dose. Missed doses are not made up. If Grade 3 toxicity recurs despite optimal supportive care, permanently discontinue pembrolizumab.
Grade 4	Permanently discontinue blinatumomab.	Permanently discontinue pembrolizumab.
*Patients requiring a delay of next cycle by >14 days due to toxicity should go off protocol therapy.		

For additional toxicity management guidance please reference Brahmer et al, “Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO clinical practice guideline” in JCO Feb 2018; the NCCN guidelines for “Management of Immunotherapy-related toxicities”); and the SITC guidelines by Puanov et al, “Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the SITC toxicity management working group” in JITC Nov 2017.

5.7.2 Management of Hematologic Toxicities

Neutropenia	Management for Blinatumomab	Management for Pembrolizumab
General principles: Neutropenia management guidelines only apply if the patient is in complete bone marrow remission. If patient is not in complete remission in the bone marrow, then blinatumomab and pembrolizumab should be continued.		
≤ Grade 1	No change.	No change in dose
Grade 2	No change.	No change in dose
Grade 3	No change. Prophylactic antimicrobials may be given per institutional standard of care.	No change. Prophylactic antimicrobials may be given per institutional standard of care.
Grade 4	If patient with documented bone marrow CR, then Withhold blinatumomab. Prophylactic antimicrobials may be given per institutional standard of care. Restart blinatumomab at previous dose when toxicity improves to <Grade 2. Missed doses/days are not made up. If patient in bone marrow CR and Grade 4 neutropenia persists for >28 days weeks despite withholding blinatumomab then permanently discontinue blinatumomab.	If patient with documented bone marrow CR, then Withhold pembrolizumab. Prophylactic antimicrobials may be given per institutional standard of care. Restart pembrolizumab when toxicity improves to <Grade 2. Missed doses are not made up. If patient in bone marrow CR and Grade 4 neutropenia persists for >28 days weeks despite withholding pembrolizumab then permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab >14 days due to toxicity should go off protocol therapy.		

Thrombocytopenia	Management for Blinatumomab	Management for Pembrolizumab
General principles: Thrombocytopenia management guidelines only apply if the patient is in complete bone marrow remission. If patient is not in complete remission in the bone marrow, then blinatumomab and pembrolizumab should be continued. Anti-platelet agents and anticoagulants should be used with caution in setting of thrombocytopenia.		
≤ Grade 1	No change.	No change.
Grade 2	No change.	No change.
Grade 3	No change.	No change.
Grade 4	If patient with documented bone marrow CR, then withhold blinatumomab. Transfuse platelets as needed per institutional standard of care. Restart blinatumomab at previous dose when toxicity improves to	If patient with documented bone marrow CR, then withhold pembrolizumab. Transfuse platelets as needed per institutional standard of care. Restart pembrolizumab when toxicity improves to <Grade 2.

Thrombocytopenia	Management for Blinatumomab	Management for Pembrolizumab
	<Grade 2. Missed doses/days are not made up. If patient in bone marrow CR and Grade 4 toxicity persists for >28 days weeks despite withholding blinatumomab then permanently discontinue blinatumomab.	Missed doses are not made up. If patient in bone marrow CR and Grade 4 toxicity persists for >28 days weeks despite withholding pembrolizumab then permanently discontinue pembrolizumab.
*Patients requiring a delay of blinatumomab >14 days due to toxicity should go off protocol therapy.		

For toxicities not meeting Grade 3 or 4 toxicity but requiring cessation of either or both drugs treatment with offending drug(s) should be permanently discontinued.

5.8 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until completion or protocol-defined therapy or until:

- Disease progression after Day 15 of Cycle 1
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.9 Duration of Follow Up

Patients will be followed every 3 months for a minimum of **2 years** after removal from or completion of treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event then for relapse and survival afterwards.

6. STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 21 days prior to registration unless otherwise stated. The screening procedures include:

6.1.1 Informed Consent

The investigator or their designee must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature. The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

Copy of signed informed consented to be faxed (858-822-1473) or emailed via secure email (JReiner@ucsd.edu) to UCSD.

6.1.2 Medical history

Complete medical, surgical and oncology history as well as history of infections are obtained at screening. Any changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

6.1.3 Demographics

Demographic profile will include date of birth, gender, race, and ethnicity.

6.1.4 Review subject eligibility criteria

Review of eligibility criteria as described in **Section 4** to ensure subject qualification for study entry.

Prior to assignment of patient study ID the below items must be emailed via secure email to the intiating site for review and approval.

1. Signed informed consent
2. Redacted source documentation required to confirm eligibility (including but not limited to):
    a. Bone marrow biopsy report
    b. Physical exam including ECOG and medical history
    c. All screening labs
    d. Chest X-Ray results
    e. Confirmation of sample to foundation one
3. Signed eligibility criteria **(Appendix D)**

All items to be emailed via secure email to (JReiner@ucsd.edu and MWieduwilt@ucsd.edu) to UCSD.

Upon receipt of all required documents, UCSD will provide subsite with patient ID and approval to intiate treatment

6.1.5 Review previous and concomitant medications

All prior medication taken by the subject within 4 weeks before starting the study is to be recorded. Concomitant medications taken by the subject during the study are to be recorded up until 28-days after last study dose. If a reportable adverse event (see **Section 8**) occurs within 28-days after last study dose, recording of concomitant medications should continue until resolution of the adverse event.

6.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height (only required at screening), and weight. Physical exam to include neurological per institutuional standard of care and testicular exam.

6.1.7 Performance status

ECOG performance status evaluated at screening and with every physical exam.

6.1.8 Adverse event assessment

Baseline assessment of subject status for determining adverse events. See **Section 8** for Adverse Event monitoring and reporting.

6.1.9 Hematology

Complete Blood Count (CBC) with differential.

6.1.10 Serum chemistries:

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin. Additional chemistries: lactate dehydrogenase (LDH), uric acid, magnesium, phosphate, TSH, T4,direct bilirubin, amylase and lipase.

6.1.11 Coagulation

Coagulation profile includes International Normalized Ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (PTT).

6.1.12 Hepatitis B, Hepatitis C and HIV serologies

Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody total, hepatitis C antibody, and HIV-1/2 Antibodies

6.1.13 Pregnancy test (for females of child bearing potential)

See **Section 4.1.9** for definition.

6.1.14 Lumbar Puncture with CSF assessments and initiation of intrathecal Methotrexate

If WBC >10,000/mcl delay procedure until WBC <10,000/mcl. CSF studies: Cell count with differential, total protein, glucose and cytology.

Intrathecal methotrexate 15 mg once

6.1.15 Disease assessment

Bone marrow aspirate and biopsy to include standard morphology, flow cytometry, karyotype, and *in situ* hybridization for t(9;22)(q34;q11.2)[BCR-ABL1]; t(v;11q23)[MLL rearranged]; t(12;21)(p13;q22)[ETV6-RUNX1]; t(1;19)(q23;p13.3)[TCF3-PBX1].

Institutional ALL FISH panel supercedes. Quantitative PCR for BCR-ABL1 p190 and p210 isoforms.

Collection of bone marrow **correlative** studies (see **Section 6.5** for details).

6.1.16 Molecular testing (FoundationOne™ Heme testing)

See **Section 6.5.1.1** for details of collection procedures.

6.1.17 Statement of Planned Allogeneic HCT

Form located in **Appendix** E to be completed and faxed or emailed via secure email to UCSD prior to starting treatment

6.1.18 Imaging

PET-CT (preferred) with diagnostic CT chest, abdomen, and pelvis with IV and oral contrast in patients with palpable lymphadenopathy or tumor masses. Patients unable to get a contrast-enhanced study should get non-contrast enhanced CT scans. If PET is not possible due to patient instability, institutional restrictions, or risk of delaying therapy then subject should undergo CT of the chest, abdomen, and pelvis without PET.

6.2 Procedures During Treatment

Lumbar puncture with intrathecal methotrexate 15 mg day 29 + 8 days during cycles 1-4 and day 38 + 8 of cycle 5 for total of 6 doses including dose given at screening. CSF studies with each lumbar puncture: Cell count with differential, cytology, and flow cytometry.

Adverse events and concomitant medications to be collected continuslously while on study.

Cycle 1

Day 1

Collection of Serum Cytokine Assay samples (See **Section 6.5**) prior to blinatumomab

Administration of Blinatumomab 9 mcg/d CIV on days 1-7 (hospital admission required per section 5.1.3)

Physical exam, performance status, vital signs, weight

Vital signs (heart rate and oxygen saturation) to be monitored continuously and full vital signs (temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation) every 4 hours during at least the intial 72 hours of blinatumomab therapy, for 72 hours after all restart or step-up doses, and for at least the initial 72 hours following the first (Cycle 1, Day 15).

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin

Adverse Event Assessment

Concomitant Medications

Day 2

Collection of Serum Cytokine Assay Samples 24 hours +/- 2 hour after start of blinatumomab (See **Section 6.5**)

Day 3

Collection of Serum Cytokine Assay samples 48 hours +/- 2 hours after start of blinatumomab (See **Section 6.5**)

Day 8

Collection of Serum Cytokine Assay samples (See **Section 6.5**) prior to increase in blinatumomab dose

Start administration of Blinatumomab 28 mcg/d CIV days 8-28

Day 9

Collection of Serum Cytokine Assay Samples 24 hours +/- 2 hour after start of blinatumomab 28 mcg/day (See **Section 6.5**)

Day 10

Collection of Serum Cytokine Assay samples 48 hours +/- 2 hours after start of blinatumomab 28 mcg/day (See **Section 6.5**)

Day 14

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Procedures: Bone marrow aspiration and biopsy. Send for standard histology, flow cytometry, cytogenetics (karyotype and *in situ* hybridization for previously documented abnormalities required, other testing per institutional standard of care) and quantitative PCR for BCR-ABL1 p190 and/or p210 if previously positive.

Correlative/exploratory research samples to be collected with bone marrow biopsy and aspirate (See **Section 6.5**)

Adverse Event Assessment

Concomitant Medications

Day 15

Collection of Serum Cytokine Assay samples (See **Section 6.5**) prior to pembrolizumab administration

Administration of Pembrolizumab 200 mg IV once

Vital signs (heart rate and oxygen saturation) to be monitored continuously and full vital signs (temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation) every 4 hours during at least the intial 72 hours of blinatumomab therapy, for 72 hours after all restart or step-up doses, and for at least the initial 72 hours following the first (Cycle 1, Day 15) and third (Cycle 2, Day 15) pembrolizumab doses.

Day 16

Collection of Serum Cytokine Assay Samples 24 hours +/- 2 hour after start of pembrolizumab (See **Section 6.5**)

Day 17

Collection of Serum Cytokine Assay samples 48 hours +/- 2 hours after start of pembrolizumab (See **Section 6.5**)

Day 21

Collection of Serum Cytokine Assay samples (See **Section 6.5**)

Day 28

Administration of Blinatumomab 28 mcg/d CIV days 8-28

Adverse Event Assessment

Concomitant Medications

Day 29 + 8 Days

Labs: CBC with Differential

Procedures: Bone marrow aspiration and biopsy. Send for standard histology, flow cytometry, cytogenetics (karyotype and *in situ* hybridization for previously documented abnormalities only) and quantitative PCR for BCR-ABL1 p190 and/or p210 if previously positive.

MRD assessment: 6-color flow cytometry on bone marrow aspirate on at least 0.5 x 10^6 mononuclear cells when technically possible. MRD assessment to be done on first pull bone marrow aspirate, redirected bone marrow aspirate should be performed as needed for first pull

bone marrow aspirate. MRD samples to be sent to University of Washington for analysis (**Section 7.1.3, Appendix C**).

Correlative/exploratory research samples to be collected with bone marrow biopsy and aspirate (See **Section 6.5**)

Lumbar puncture with **Methotrexate administration** and CSF studies: Cell count with differential, cytology, and flow cytometry.

Imaging: Diagnostic CT chest, abdomen, and pelvis with IV and oral contrast in patients with palpable lymphadenopathy or masses at diagnosis. Patients unable to get contrasted study should get non-contrasted CT scans.

Adverse Event Assessment

Concomitant Medications

Day 36

Administration of Pembrolizumab 200 mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Cycle 2

Day 1

Administration of Blinatumomab 28 mcg/d CIV days 1-28

Physical exam, performance status, vital signs, weight

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Day 15

Administration of Pembrolizumab 200 mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Day 29 + 8 Days

Labs: CBC with differential

Procedures: Bone marrow aspiration and biopsy. Send for standard histology, flow cytometry, cytogenetics (karyotype and *in situ* hybridization for previously documented abnormalities required, additional testing allowed per institutional standard of care) and quantitative PCR for BCR-ABL1 p190 and/or p210 if previously positive.

Correlative research samples to be collected with bone marrow aspirate and peripheral blood for flow cytometry and bone marrow aspirate for western blot (See **Section 6.5**)

MRD assessment: 6-color flow cytometry on bone marrow aspirate on at least 0.5 x 10^6 mononuclear cells when technically possible. MRD assessment to be done on first pull bone marrow aspirate, redirected bone marrow aspirate should be performed as needed for first pull bone marrow aspirate. MRD samples to be sent to University of Washington for analysis (**Section 7.1.3, Appendix C**).

Lumbar puncture with **Methotrexate administration** and CSF studies: Cell count with differential, cytology and flow cytometry.

Imaging: Diagnostic CT chest, abdomen, and pelvis with IV and oral contrast in patients with palpable lymphadenopathy or masses at diagnosis. Patients unable to get contrasted study should get non-contrasted CT scans.

Day 36

Administration of Pembrolizumab 200 mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Cycles 3 and 4

Day 1

Administration of Blinatumomab 28mcg/d CIV days 1-28

Physical exam, performance status, vital signs, weight

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase, lipase, TSH and T4 (cycles 3 only).

Adverse Event Assessment

Concomitant Medications

Day 15

Administration of Pembrolizumab 200mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Day 29 + 8 Days

Labs: CBC with differential

Procedures: Bone marrow aspiration and biopsy. Send for standard histology, flow cytometry, cytogenetics (karyotype and *in situ* hybridization for previously documented abnormalities required, additional testing allowed per institutional standard of care) and quantitative PCR for BCR-ABL1 p190 and/or p210 if previously positive.

MRD assessment: 6-color flow cytometry on bone marrow aspirate on at least 0.5 x 10^6 mononuclear cells when technically possible. MRD assessment to be done on first pull bone marrow aspirate, redirected bone marrow aspirate should be performed as needed for first pull bone marrow aspirate. MRD samples to be sent to University of Washington for analysis (**Section 7.1.3, Appendix C**).

Lumbar puncture with **Methotrexate administration** and CSF studies: Cell count with differential, total protein, random glucose, cytology.

Adverse Event Assessment

Concomitant Medications

Day 36

Administration of Pembrolizumab 200mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Cycle 5

Day 1

Administration of Blinatumomab 28mcg/d CIV days 1-28

Physical exam, performance status, vital signs, weight

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase, lipase, TSH and T4.

Adverse Event Assessment

Concomitant Medications

Day 15

Administration of Pembrolizumab 200mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

Day 36

Administration of Pembrolizumab 200mg IV once

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Adverse Event Assessment

Concomitant Medications

6.2.1 End of Treatment Visit (Day 38 + 8 days of Cycle 5)

On Day 38 + 8 days of Cycle 5:

Physical exam, performance status, vital signs, weight

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin, amylase and lipase

Procedures: Bone marrow aspiration and biopsy. Send for standard histology, flow cytometry, cytogenetics (karyotype and in situ hybridization for previously documented abnormalities only) and quantitative PCR for BCR-ABL1 p190 and/or p210 if previously positive.

MRD assessment: 6-color flow cytometry on bone marrow aspirate on at least 0.5 x 106 mononuclear cells when technically possible. MRD assessment to be done on first pull bone marrow aspirate, redirected bone marrow aspirate should be performed as needed for first pull bone marrow aspirate. MRD samples to be sent to University of Washington for analysis (**Section 7.1.3, Appendix C**).

Imaging: Diagnostic CT chest, abdomen, and pelvis with IV and oral contrast in patients with palpable lymphadenopathy or masses at diagnosis. Patients unable to get contrasted study should get non-contrasted CT scans.

Lumbar puncture with **Methotrexate administration** and CSF studies: Cell count with differential, cytology, and flow cytometry.

Adverse Event Assessment

Concomitant Medications

6.3 Follow-up Procedures

Patients will be followed for a minimum of 2 years from study entry or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients taken off study to undergo allogeneic or autologous stem cell transplantation will be censored for relapse and survival as of the date they begin non-protocol therapy. Patients refusing protocol-defined follow-up or lost to follow-up will be censored as to their status on the day of last contact.

Patients will be seen every 3 months for 2 years after completion of therapy. At these visits the following assessment will be performed:

Physical exam, vital signs, weight

Labs: CBC with differential

Concomitant Medications

6.4 Relapse

At suspected or documented relapse the following assessments should be performed:

Physical exam with vital signs, and weight.

Labs: CBC with differential, CMP (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total bilirubin, AST, ALT, alkaline phosphatase), direct bilirubin

Bone marrow aspiration and biopsy. Send for standard histology, flow cytometry, cytogenetics (karyotype and *in situ* hybridization) and quantitative PCR for BCR-ABL1 p190 and p210 if previously positive.

Molecular testing (FoundationOne™ Heme testing)
See **Section 6.5.1.1** for details of collection.

Lumbar puncture with CSF studies: Cell count with differential, cytology and flow cytometry.

Imaging: Diagnostic CT chest, abdomen, and pelvis with IV and oral contrast in patients with history of palpable lymphadenopathy or masses at diagnosis or palpable lymphadenopathy or masses at relapse. Patients unable to get contrasted study should get non-contrasted CT scans.

Concomitant Medications

6.5 Correlative Studies

The goal of the planned laboratory correlative studies is to determine PD-L1 and PD-L2 protein expression on lymphoblasts and in the bone marrow microenvironment at diagnosis, to determine changes in PD-L1 and PD-L2 expression with blinatumomab exposure, and correlate changes in PD-L1 and PD-L2 expression with disease response. We also aim to determine how changes in cytokine expression with therapy correlate with PD-L1 and PD-L2 expression changes.

6.5.1 Sample Collection Guidelines

All samples collected must be labeled with study ID, Patient ID number, date of collection, time point of collection and time of collection.

6.5.1.1 Molecular testing (FoundationOne™ Heme testing)

Bone marrow samples will be sent for FoundationOne™ Heme mutational analysis at diagnosis and at time of relapse.

If a patient's health insurance will not cover the cost of FoundationOne Heme Testing then a sample should not be sent. This will not be considered a protocol deviation.

Research requisition form for samples available in **Appendix B.**

Samples collection guidelines:

Bone marrow aspirate (preferred):

Collect 0.5 to 2 mL bone marrow aspirate in an EDTA tube.

Peripheral blood:

If unable to obtain bone marrow aspirate and patient has peripheral blood blast count >20%, then send peripheral blood for mutational analysis as follows:

Collect 10 mL whole blood in EDTA, sodium citrate, or sodium heparin tube.

Bone marrow core biopsies:

If unable to provide adequate bone marrow aspirate or peripheral blood sample, then provide formalin-fixed paraffin embedded bone marrow core biopsy sample.

Formalin-fixed paraffin-embedded (FFPE) block OR 14 unstained slides + 1 haematoxylin + eosin stained slide.

Note: EDTA recommended for decalcification for the minimum amount of time. Hydrochloric acid and formic acid should not be used for dec

Shipping instructions:

Place the FoundationOne Heme Requisition Form (**Appendix B**) and samples into the FoundationOne Heme Specimen Kit.
Place the FoundationOne Heme Specimen Kit (including the FoundationOne Heme Requisition Form) into the provided shipping pack and seal the shipping pack.
3. Complete the pre-printed shipping labels (if necessary) and apply to shipping pack.
4. Ship completed specimen kit (requisition form, samples) to:

Accessioning, Clinical Laboratory Foundation Medicine, Inc.
150 Second Street Cambridge, MA 02141
Phone: 617-418-2200 Fax: 617-418-2290

Place all materials into the FedEx pack provided with the Specimen Kit and drop pack at your site's designated FedEx pick up location or call FedEx to schedule a pick up.

6.5.1.2 Lymphoblast PD-L1 and PD-L2 expression by Western Blot (UCSD)

Bone marrow aspirate samples for FACS of lymphoblasts and PD-L1 and PD-L2 expression by Western blotting will be collected at the following time points and shipped to the laboratory of Gerald Morris, MD, PhD:

At screening
Cycle 1 Day 14

Cycle 1 Day 29 +8 days

In the case of a dry tap, a core biopsy is to be collected.

Complete Sample Collection CRF (Appendix F) for each shipment. Email the completed Sample collection CRF prior to shipment to JReiner@ucsd.edu

- Make a copy of the form to include with the sample(s)
- Retain the original at the site for your records

Email a de-identified (redacted) pathology report(s) if available. Write the study ID on the top of each page of the pathology report.

Samples to be shipped overnight to the Morris Laboratory for processing and analysis:

Gerald Morris, MD, PhD
Department of Pathology
University of California San Diego
249A Leichtag Family Foundation Biomedical Research Building
9500 Gilman Drive
La Jolla, CA 92093
Ph: 858-822-3490

Email: gpmorris@ucsd.edu

6.5.1.3 T-cell subsets, PD-1 and PD-L1 expression studies by Flow Cytometry

Bone marrow aspirate and peripheral blood samples for flow cytometry for T-cell subsets, PD-1 on T-cells and PD-L1 on lymphoblasts along with appropriate patient-specific lymphoblast markers.

Minimum flow cytometry panels as follows:

Peripheral blood T-cells:
Panel 1 (identification.activation panel) - live/dead stain, CD3, CD4, CD8, CD16, CD56, OX40, CD137, PD-1, LAG-3, TIM-3
Panel 2 (Treg panel) - live/dead stain, CD4, CD25, FoxP3 (intracellular)
Panel 3 (NK cells) - live/dead stain, CD3, CD4, CD8, CD16, CD56, IFN-g (intracellular), granzyme-B (intracellular)

Bone marrow lymphoblasts: PD-L1, CD19, CD10*, TdT*, 7-AAD
(Note: *lymphoblast markers to be selected based on initial immunophenotype and may also include CD34, cCD22, sCD22, CD24, Pax5, CD79a)

Aspirate samples will be sent for testing at the following time points:

At screening
Cycle 1 Day 14
Cycle 1 Day 29 + 8 days
Cycle 2 Day 29 + 8 days

3-5 mL of bone marrow aspirate and 5 mL peripheral blood to be collected in EDTA (lavender-top) tube and be sent same day by hand delivery or overnight shipping to the laboratory of Gerald Morris, MD, PhD:

Gerald Morris, MD, PhD
Department of Pathology
University of California San Diego
249A Leichtag Family Foundation Biomedical Research Building
9500 Gilman Drive
La Jolla, CA 92093
Ph: 858-822-3490
Email: gpmorris@ucsd.edu

In the case of a dry tap, a core biopsy is to be collected.

6.5.1.4 Serum cytokine assays

Peripheral blood Serum Cytokine assays samples will be collected at the following time points in Cycle 1:

Day 1 (prior to blinatumomab)
Day 2 (24 +/- 2 hours after blinatumomab start)
Day 3 (48 hours +/- 2 hours after blinatumomab start)
Day 8 (prior to blinatumomab 28 mcg/day dose)
Day 9 (24 +/- 2 hours after blinatumomab dose increase on Day 8)
Day 10 (48 hours +/- 2 hours after blinatumomab dose increase on Day 8)
Day 15 (prior to pembrolizumab)
Day 16 (24 +/- 2 hours after pembrolizumab Day 15 dose)
Day 17 (48 +/- 2 hours after pembrolizumab Day 15 dose)
Day 21

This study will utilize the Cytokine Human 10-plex panel for Luminex® Platform which measures levels of GM-CSF, TNF-α, IL-2, IL-1β, IL-4, IL-6, IL-8, IFN-γ, IL-10, IL-5.

Peripheral blood to be collected in 1-10mL EDTA tube. Sample to be processed at 1200g for 10min and the plasma stored at -70C. Samples may be batch shipped after collection of all samples for each patient have been collected. Please ensure that a completed CRF form (appendix F) is included with each sample.
Samples to be shipped to UCSD overnight on dry ice.

Study Coordinator, BMT Clinical Trials
UCSD Moores Cancer Center
3855 Health Sciences Drive, Room 2024
La Jolla, CA 92093
Tel: 858-822-5364/6396/6397

Samples to be stored at the UCSD Moores Cancer Center Clinical Trials office until analyzed in Dr. Morris's Lab at UCSD.

6.6 Removal of Subjects from Study Treatment and Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

1. Patient completed study treatment;
2. Patient voluntarily withdraws from treatment (follow-up permitted);
3. Patient withdraws consent (termination of treatment and follow-up);
4. Patient is unable to comply with protocol requirements;
5. Patient demonstrates disease progression;
6. Patient experiences toxicity that makes continuation in the protocol unsafe;
7. Treating physician judges continuation on the study would not be in the patient's best interest;
8. Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
9. Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
10. Lost to follow-up.
    If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

7. Measurement of Effect

7.1 Assessment of disease response

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline who have received at least one cycle of therapy and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

7.1.2 Disease Parameters

Measurable disease.

Bone marrow:

Detectable disease by standard morphology, immunohistochemistry, and/or flow cytometry.

M1: <5% lymphoblasts
M2: ≥5% but ≤25% lymphoblasts
M3:>25% lymphoblasts

Minimal residual disease: To be assessed by a minimum of 6-color flow cytometry with each bone marrow aspiration and biopsy on a minimum of 0.5×10^6 mononuclear cells when technically possible.

Peripheral blood:

Detectable disease by standard morphology (peripheral blood smear) and/or flow cytometry.

Extramedullary disease:

Lymph node enlargement: measurable (pathologically enlarged) lesions are lymph nodes with short axis diameter >10 mm except for submental and submandibular nodes which are measurable (pathologically enlarged) if >15 mm in short axis and retropharyngeal nodes which are measurable if >8 mm.

Extramedullary masses outside of lymph nodes: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, X-ray) or as ≥10 mm with spiral CT scan. All tumor and lymph node measurements must be recorded in millimeters (or decimal fractions of centimeters).

CNS Disease: Will be assessed by cell count and cytology at screening, with each intrathecal chemotherapy treatment, and at suspicion for new or worsening CNS disease.

Definitions of CNS disease status:

CNS-1: No lymphoblasts in the CSF
CNS-2: WBC <5/microliter with presence of lymphoblasts in CSF
CNS-3: WBC ≥5/microliter with presence of lymphoblasts in CSF or cranial nerve deficit

If lumbar puncture is traumatic in a patient with circulating blasts and CSF WBC is ≥5 cells/mcL in CSF with blasts, calculate the CSF and blood WBC/RBC ratios. If the CSF WBC/RBC ratio is at least two-fold greater than the blood WBC/RBC ratio, then classify as CNS-3; if less than two-fold greater, then it is CNS-2.

Non-measurable disease. All other lesions (or sites of disease), including small extra-nodal lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, leukemia/lymphoma cutis, abdominal masses (not followed by CT), hepatomegaly, splenomegaly, testicular masses, gum infiltration, and cystic lesions are all considered non-measurable.

7.1.3 Methods for Evaluation of Measurable Disease

Bone marrow:
Bone marrow aspiration of 2-3 ml should be prepared for standard morphologic evaluation by aspirate smears on glass slides. Additional aspirate (5-10 mL) should be obtained for flow cytometry, cytogenetics (karyotype and *in situ* hybridization), and molecular analyses.

Bone Marrow Aspirate or Biopsy samples to be collected at study specified time points and sent to the University of Washington for MRD analysis (see **Appendix C**). MRD assessment to be done on first pull bone marrow aspirate. If necessary, aspirate needle should be re-directed to obtain first pull aspirate for MRD studies.

This analysis is to be performed on all patients, and billed to their insurance.

Requisition form for samples available in **Appendix C.**

If bone marrow aspirate cannot be obtained (dry tap) or no spicules present in aspirate, 2 bone marrow core biopsies should be obtained for flow cytometry and cytogenetics. Institutional practice supersedes.

Bone marrow core needle biopsy should be 1-2 cm in length for adequate evaluation.

Blood:
Evaluation of peripheral blood should occur by morphologic evaluation of a peripheral blood smear. This should be performed at the time of each bone marrow biopsy and when clinically indicated.

Extramedullary Disease

Lymph node enlargement, tumors:
For patients with a known mediastinal mass or lymphadenopathy or palpable masses on physical exam, FDG-PET/CT scan will be performed with diagnostic CT scans of the chest, abdomen, and pelvis with IV contrast except when contraindicated or felt unsafe by the investigator. When PET-CT not feasible, CT chest/abdomen/pelvis with contrast alone should be performed.

For patients with pathologic lymph node enlargement or tumors, all measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 14 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

CNS disease:
CSF samples from lumbar punctures should be sent for cell count, total protein, glucose, and standard cytology with every lumbar puncture performed while patient remains on study.

Effusions:
When safe to do so, pleural effusions and ascites should be sampled and analyzed by standard cytology for evidence of disease.

Cytologic evaluation of any effusion that appears or worsens during treatment when the measurable tumor has otherwise met criteria for complete response or stable disease is mandatory to differentiate between complete response and progressive disease.

7.1.4 Response Criteria

Response criteria for bone marrow, blood, CNS disease, and mediastinal disease are from NCCN Guidelines for Acute Lymphoblastic Leukemia, Version 1.2015, 06/11/15.

Response criteria for lymph node and other extramedullary disease are derived from International Working Group revised response criteria for malignant lymphoma [17].

7.1.4.1 Bone Marrow and Blood

Complete Response (CR):
- -No circulating blasts or extramedullary disease
- -Bone marrow with normal trilineage hematopoiesis and <5% blasts
- -Absolute neutrophil count (ANC) >1,000/microliter
- -Platelet count >100,000/microliter
- -No disease recurrence for 28 days

Complete Response with Partial Hematologic Recovery (CRh):
- -As for CR but platelet count >50,000/microliter, hemoglobin >7 g/dL, and ANC >500/microliter

Overall Response Rate (ORR):
- -Defined as the sum of the CR rate and CRh rate.

Refractory disease:
- -Failure to achieve CR at end of induction

Progressive Disease (PD):
- -Increase of at least 25% in the absolute number of circulating or bone marrow leukemic blasts or appearance of new extramedullary disease

Relapsed Disease:
- -Re-appearance of blasts in the bone marrow (>5%) or blood or in any extramedullary site after achieving a CR or CRh

Flow MRD Negativity:
- -Absence of detectable leukemic blasts above the 0.01% (1x10-4) level by minimum 6-color flow cytometry

7.1.4.2 CNS Disease

CNS Remission:
- -Achievement of CNS-1 disease status in a patient with CNS-2 or CNS-3 disease status at diagnosis

CNS Relapse:

-New development of CNS-3 disease status or clinical signs of CNS involvement such as cranial nerve palsy, brain involvement, eye involvement, or hypothalamic syndrome. Whenever possible, clinical signs of CNS involvement without concomitant CSF involvement should be confirmed by biopsy. Otherwise, attribution of CNS symptoms to leukemia/lymphoma and requirement for treatment will be based on investigator judgment.

7.1.4.3 Mediastinal Disease

Complete Response:

- Complete resolution of mediastinal enlargement by CT or if FDG-avid/PET positive prior to therapy, mass of any size permitted if PET negative

Complete Response Unconfirmed (CRu):

- Residual mediastinal enlargement that has regressed by >75% in the sum of the product of the greatest perpendicular diameters (SPD)

Partial Response (PR):

- >50% decrease in the SPD of the mediastinal enlargement

Progressive Disease (PD):

- >25% increase in the SPD of the mediastinal enlargement

No response (NR):

- Failure to qualify for CR, CRu, PR, or PD

Relapse:

-Recurrence of mediastinal enlargement after achieving CR or Cru

7.1.4.4 Nodal Disease

Complete Response:

- Complete resolution of lymph node enlargement by CT or, if FDG-avid or PET positive prior to therapy, lymph node enlargement of any size permitted if PET negative

Partial Response (PR):

- ≥50% decrease in the SPD of up to 6 largest dominant masses with no increase in size of other nodes

Progressive Disease (PD) or Relapse:

- any new enlarged lymph node mass >1.5 cm in any axis, ≥50% increase in the SPD of more than one node, or ≥50% increase in the longest diameter of a previously identified node >1 cm in short axis
- lesions PET positive if FDG-avid or PET positive prior to therapy

No response (NR):

- Failure to qualify for CR, PR, or PD

7.1.4.5 Other Extramedullary Disease (e.g. Spleen, Liver)

Complete Response:
- Complete resolution of disease by CT or, if FDG-avid or PET positive prior to therapy, lymph node enlargement of any size permitted if PET negative

Partial Response (PR):
- ≥50% decrease in the SPD of up to 6 largest dominant masses with no increase in size of other masses. If single mass then ≥50% decrease in greatest transverse diameter. No increase in size of liver or spleen.

Progressive Disease (PD) or Relapse:
- >50% increase from nadir in the SPD of any previous lesions

No response (NR):
- Failure to qualify for CR, PR, or PD

7.1.5 Duration of Response

The duration of overall response is measured from the date that measurement criteria are met for CR/CRh until the first date that relapsed disease is objectively documented.

7.1.6 Relapse-Free Survival

Relapse-free survival (RFS) is defined as the duration of time between objective documentation of CR/CRh and relapse of disease or death in CR.

7.1.7 Overall Survival

Overall survival is defined as the duration of time from start of treatment to death from any cause.

7.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (http://ctep.cancer.gov/reporting/ctc.html) for reporting of (non-hematologic) adverse events.

8. ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins after initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in **Section 8.3.**

All patients experiencing an adverse event, regardless of its relationship to study drug {or <u>at least possibly</u> related to the drug}, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death

8.2 Severity

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

Moderate (grade 2): the event causes discomfort that affects normal daily activities.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

Life-threatening (grade 4): the patient was at risk of death at the time of the event.

Fatal (grade 5): the event caused death.

8.3 Seriousness

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death.
   If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening.
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

8.4 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

8.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Investigator's Brochure or Product Label for blinatumomab or pembrolizumab.

8.6 Reporting of Overdose to the Sponsor, to Merck and to Amgen

For 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 to:

Merck Global Safety
Attn: Worldwide Product Safety
FAX 215 993-1220

And

Amgen SAE
Fax: 888-814-8653

8.7 Reporting of Pregnancy and Lactation to the Sponsor, to Merck and to Amgen

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 completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. 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). If the pregnancy continues to term, the outcome (health of infant) must also be reported.
Such events must be reported within 24 hours to the Sponsor and to:

Merck Global Safety
Attn: Worldwide Product Safety
FAX 215 993-1220

And

Amgen SAE
Fax: 888-814-8653

8.8 Reporting Requirements for Adverse Events

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document (see **Appendix G** in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

8.8.1 Expedited Reporting

A. The **Study Chair** and **Site Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

- The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug. Serious Adverse Event (SAE) reporting will be in accordance with the UCSD IRB Regulations and Code of Federal Regulation Title 21 Volume 5 Part 312.32. MedWatch forms will be utilized for reporting purposes. For a copy of the form, go to http://www.fda.gov/medwatch/getforms.htm.
- All SAEs from outside institutions must be reported to UCSD BMT Clinical Trials Office within 24 hours of learning of its occurrence, even if it is not felt to be treatment related. Follow-up information about a previously reported SAE must be sent to the UCSD BMT Clinical Trials Office as soon as complete details of the SAE are known.

UCSD BMT Clinical Trials Office
3855 Health Science Drive MC0698
La Jolla, CA, 92093,
Phone: 858-822-5364,
Fax 858-822-1473
Email : jreiner@ucsd.edu; mwieduwilt@ucsd.edu

- If the SAE is death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the UCSD DSMB Chair by the UCSD Clinical Trials Office within 24 business hours. The reporting procedure is by personal communication via phone or with written documentation of the one to one communication via e-mail, with a copy of the e-mail to DSMB Administrator and DSMB Coordinator.
- Follow-up data should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation.

B. Merck and Amgen must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

8.8.1.1 Immediate Reporting of Adverse Events to the Sponsor, to Merck and to Amgen

Any serious adverse event, 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 or Amgen product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety and Amgen.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and Amgen and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck or Amgen 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, Amgenand 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

SAE reports and any other relevant safety information are to be forwarded to the Amegen SAE facsimile number: +1-888-814-8653

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 outcome.

8.8.1.2 Events of Clinical Interest

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

Events of clinical interest for this trial include:
1. An overdose of Merck product, as defined in Section 8.6 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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).

1. Additional adverse events:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in Appendix G and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Merck Global Safety
Attn: Worldwide Product Safety
FAX 215 993-1220

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

C. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.

2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.

3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.

4. Any new information (e.g., publication, safety monitoring report, updated

sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.

5. Any breach in confidentiality that may involve risk to the subject or others.

6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

8.9 UC San Diego IRB Notification of SAEs

The Institutional Review Board (IRB) of record at UC San Diego will be notified of all SAEs by the study chair, or their designee, based on the UCSD IRB standard operating procedures

- The UCSD Human Research Protections Program (HRPP) must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
  4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
  5. Any breach in confidentiality that may involve risk to the subject or others.
  6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

D. The **FDA** must be notified according to the following timelines:

- Within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- Within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

8.9.1 Routine Reporting Requirements

A. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

B. The **IRB of record at UC San Diego** will be notified of all non-UPRs from all sites by the study chair at the time of the continuing review..

C. The **FDA** must be notified of all non-serious adverse events annually at the time of the annual report.

9. AGENT INFORMATION

9.1 Blinatumomab

Please refer to the Pharmacy Information Guide for more comprehensive information.

Other names for the drug: AMG-103

Mechanism of action (or Product description): Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

Availability: provided by sponsor free of charge

How supplied:
Blinatumommab is provided in 4mL single use glass injection vials as sterile, preservative free, white to off-white lyophilized powder for reconstitution and administration by intravenous infusion. Each vial contains a target of 38.5 mcg blinatumomab. Following reconstitution with 3mL sterile water for injection (SWFI), the final concentration of blinatumomab will be 12.5mcg/mL.

IV solution stabilizer (IVSS) is provided in 10mL single use glass injection vials as a sterile, preservative free, clear, colorless-to-slightly yellow liquid concentrate.

Storage and stability:
Blinatumomab and IVSS are to be stored in original packaging, under refrigeration at 2 degrees Celsius to 8 degrees Celsius and protect from light until time of use. Do not freeze.

Refer to the Pharmacy Information Guide for information regarding storage of intact vials, reconstituted vials and finished doses.

Preparation:
Refer to the Pharmacy Information Guide for dose preparation information.

Route of administration for this study:
Administer blinatumomab as a continuous intravenous infusion at a constant flow rate using an infusion pump. The pump should be programmable, lockable, non-elastomeric, and have an alarm.

Blinatumomab must be administered using IV tubing that contains a sterile, non-pyrogenic, low protein-binding, 0.2 micron in-line filter for 24 and 48 hour infusion bags. An in-lline filter is not required for a 7 day infusion bag. The following materials are considered compatible with blinatumomab: polyolefin/polyethylene, ethylene vinyl acetate (EVA), or PVC non-DEHP components.

Side effects:
Cytokine release syndrome, hypotension, fever, respiratory distress, encephalopathy, confusion, seizure, infection, tumor lysis syndrome, neutropenia, febrile neutropenia, transaminitis.

9.2 Pembrolizumab

Please refer to Investigator's Brochure for more comprehensive information.

Other names for the drug: MK-3475

Mechanism of action (or Product description): Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Availability: provided by sponsor free of charge

How supplied: Pembrolizumab is a sterile-filtered liquid and is aseptically filled into single-use vials. Each vial contains 4 mL of sterile solution for IV infusion, 25 mg/mL pembrolizumab, and a total of 100 mg protein/vial.

Storage and stability:
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze.

Storage of Reconstituted and Diluted Solutions
The product does not contain a preservative.

If the diluted pembrolizumab solution is not used immediately, it may be stored for no more than 24 hours at 2°C to 8°C. This 24-hour total hold time may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or IV bags must be allowed to come to room temperature before use.

Preparation:
Dilute pembrolizumab with 0.9% sodium chloride of dextrose 5% to a concentration of 1 to 10mg/mL prior to administration.

See Pharmacy Manual for additional information.

Route of administration for this study:

Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. Do not co-administer other drugs through the same infusion line.

Side effects:
Most common adverse reactions (reported in ≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

9.3 Methotrexate (Intrathecal)

Other names: Rheumatrex®, Trexall®

Type of agent: Anti-metabolite, anti-folate

Mode of action: Inhibition of folate metabolism through irreversible inhibition of dihydrofolate reductase

Storage & Stability: Once diluted, methotrexate is stable for 24 hours at 21°-25°C.

Protocol dose:
Intrathecal: 15 mg in preservative-free normal saline

Preparation: Reconstitute in D_5W or NS

Route of administration: Oral, intravenous, and intrathecal administration. This protocol will use IV methotrexate over 4 hours. Intrathecal methotrexate is administered by syringe by slow push.

Availability: Commercially available as powder in single use vials of 20 and 1000 mg or as liquid vials of 50 and 250 mg. Oral tablets available as 2.5, 5, 7.5, 10, and 15 mg tablets.

Toxicity: Bone marrow suppression, stomatitis/enteritis, transaminitis, cutaneous reaction, renal failure, pneumonitis, arachnoiditis, motor paralysis, cranial nerve palsy, seizure, coma, demyelinating encephalopathy, hyperuricemia, oligospermia, stomatitis, nausea, vomiting, diarrhea, mucositis, intestinal perforation, immunosuppression.

9.3.1 Return and Retention of Study Drug

Remaining drug is to be destroyed, according to Moores Cancer Center Investigational Drug Services destruction policy or the institutional policy of the individual participating institutions. Drug accountability and record of drug destruction must be provided to UCSD BMT Clinical Trials Office.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a Phase I/II single-arm, open-label, multicenter study of pembrolizumab in combination with blinatumomab. This study includes a Phase I safety run-in of 3-6 patients followed by accrual of 18-21 additional patients for a total of 24.

10.2 Sample Size and Accrual

Patients presenting to outpatient clinics and inpatient settings or existing patients at participating sites with relapsed or refractory B-lineage ALL will be approached by treating providers or their representatives regarding interest in trail participation.

The accrual goal is 24 patients. Rationale for accrual goal is outlined in **Section 10.5.1**

10.3 Enrollment targets by race/ethnicity and sex

Accrual Targets (for maximum accrual)			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	4	5	9
Not Hispanic or Latino	6	9	15
Ethnic Category: Total of all subjects	10	15	24
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	1	2
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	9	11	20
Racial Category: Total of all subjects	11	14	24

10.4 Evaluable Subjects and Subject Replacement

Stage 1 (Safety evaluation)

Evaluable subjects are defined as any patient receiving the combination of blinatumomab and pembrolizumab starting day 15 of Cycle 1. The DLT monitoring period will be 28 days starting Day 15 of Cycle 1. Subjects withdrawing from investigational treatment during the 28 day DLT monitoring period for a reason that is definitely unrelated to toxicity of the study agent (e.g. disease progression, patient withdrawal of consent) will be replaced for the safety anaylsis. 3-6 patients will be enrolled at in Stage 1 as determined by 3+3 rules. These patients will also be evaluated for efficacy.

Stage 2

Stage 2 of the study will include an expansion cohort of up to 21 additional subjects for a total of 24 subjects to evaluate the efficacy of the combination of blinatumomab and pembrolizumab. All patients receiving combination therapy starting day 15 of cycle 1 will be considered evaluable for overall response rate of entire population, RFS and OS.

10.5 Data Analyses Plans

10.5.1 Primary Analysis

Simon's 2-stage for efficacy

We plan a Simon's 2-stage MiniMax design evaluation of the combination of blinatumomab and pembrolizumab in relapsed or refractory B-cell ALL with >50% blasts in the marrow.

We assessed the sample size for studying using overall response rate (CR + CRh) . From recent large Phase II study including 189 subjects with relapsed/refractory B-lineage ALL, ORR (CR + CRh) to blinatumomab monotherapy was approximately 29% in patients with >50% lymphobalsts in the bone marrow (Topp et al. 2015). Response rates for PD-1 inhibitors in relapsed or refractory ALL are unknown but given mechanism of action it likely approaches zero.

An absolute increase in the overall response rate of 25 percentage points (i.e. to 54% ORR in patients evaluable for efficacy) or greater will demonstrate sufficient activity to consider the regimen for further study.

To calculate sample sizes for Stage 1 and Stage 2 we used a probablility of type I error (α) = 0.05 and a power (1-β) = 0.80 with p0=0.29 and p1=0.54.

The null hypothesis that the true response rate is 0.29 will be tested against a one-sided alternative. In the first stage, 18 patients evaluable for efficacy will be accrued. If there are 7 or fewer responses in these 18 patients, the study will be stopped. Otherwise, 6 additional patients will be accrued for a total of 24 patients evaluable for efficacy of the combination. The null hypothesis will be rejected if 11 or more responses are observed in 24 evaluable patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true response rate is 0.54. The likelihood of early termination is 0.88, if the null hypothsis is true.

Safety rules

At the time of the Stage 1 effiicacy analysis, all patients will be reviewed again for DLTs as defined in Section 5.1.4 occurring at any time during therapy.

A DLT rate exceeding 0.3 will be considered unacceptable. The first 3, 6, 12, and 24 patients will be monitored for DLTs. The first 6 pateints will be monitored every other week. The next 6 pateints will be monitored monthly. Subsequent patients will be monitored every other month.

k	**1**	**2**	**3**	**4**
n_k	3	3	6	12

N_k	3	6	12	24
r_k	1	1	3	5

Table: Monitoring design for DLTs. The stage is denoted by k. The number of patients accrued during and up to stage k are denoted by n_k and N_k respectively. The critical value at stage k is denoted by r_k.

If the critical value r_k for any stage is exceeded, study enrollment will be suspended and a discussions between the study chair, study principal investigators, the DSMB for the study, and the FDA will occur to discuss amending or closing the study.

10.5.2 Secondary Analyses

Complete response rate, overall response rate (CR + CRh), MRD negativity rate in patients achieving a CR or CRh, allogeneic HCT rate, and rates of adverse events will be reported using descriptive statistics. Relapse-free survival and overall survival will be estimated using the Kaplan-Meier method. Correlation between PD-L1 and PD-L2 expression and response to the combination of blinatumomab and pembrolizumab and correlation of changes in PD-L1 and PD-L2 expression with cytokine response will be evaluated with Chi-squared analysis.

11. STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to UCSD conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

The IRB should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the UC San Diego Clinical Trials Office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Required Documentation (For multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Research Office.

- A copy of the official IRB approval letter for the protocol and informed consent document OR documentation of agreement to accept UCSD IRB approval of the protocol and consent through the UC IRB Reliance Registry by means of the UC Memorandum of Understanding
- IRB membership list or FWA letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- A copy of the IRB approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.5 Registration Procedures

All patients must obtain a study ID number from the UCSD BMT Clinical Trials Office before enrollment to study in the Velos EDC system. An eligibility check list signed by the PI or Sub-I must be faxed or emailed via secure email to the BMT Clinical Trials Office at 858-822-1473 or JReiner@ucsd.edu. Confirmation of eligibility is required prior to starting treatment.

Patients will be given a unique sequential patient ID number based on the study number, site number and patient enrollment number (1504-XX-XX).

UCSD BMT Clinical Trials Office staff will notify the outside site by fax or email via secure email of the patient's study number, and the randomization group of the patient.

Patient Eligibility Check list is located in **Appendix D**.

11.6 Data Forms and Submission Schedule

Data Forms Completion

- Data forms are to be completed following Screening, and then after each study visit.

Data Forms Submission

Data forms are to be completed in the Velos EDC system and corresponding source documentation uploaded within 2 weeks after each study visit. Timeline for Data Form submission is as follows:

- Screening Forms: to be completed within 24 hours following confirmation of eligibility and enrollment on the study.
- Treatment Visit Forms: within 2 weeks of the end of each visit, to include Con Med forms.
- Off-Study Form/Death Form: within 1 week of knowledge of off-study status or death of patient.
- AE Forms: to be updated at least every 2 weeks, but always prior to scheduled Study Conference Calls (scheduled monthly)
- SAE Forms: to be sent within 24 hours of knowledge of the event, and then as soon as a final report can be done.

11.7 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

11.8 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the Study Chair, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be every 6 months.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported annually and will include:

1) the protocol title, IRB protocol number, and the activation date of the study.
2) the number of patients enrolled to date
3) the date of first and most recent patient enrollment
4) a summary of all adverse events regardless of grade and attribution
5) a response evaluation for evaluable patients when available
6) a summary of any recent literature that may affect the ethics of the study.

11.9 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

11.9.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

11.9.2 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion.

A. Major violations must be reported to the IRB within 10 working days of awareness of the violation.

Major violations include:

- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

B. Minor violations may be reported to the IRB at the time of the continuing review. Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

11.10 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Study Chair. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB of record at UC San Diego for approval prior to implementation.

11.11 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all

study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.12 UCHMC Data and Publication Policy

Overview

The process of preparation, clearance, and publication of any manuscript which results from a UCHMC study is complete when the study results are disseminated to the scientific community by means of a formal referred publication. The UCHMC Steering Committee has oversight over the use and publication of UCHMC data. Each institution participating in protocol studies must be acknowledged and each contributing institution should have the opportunity to review the manuscript.

Data rights and access

The study chair has sole rights to the data and data is not to be reviewed or accessed without the written approval of the study chair.

Publication Preparation and Review

The responsibility for writing manuscripts describing a UCHMC study belongs to the Study Principal Investigator. The Biostatistics Core provides analytic assistance and review for manuscripts based on UCHMC clinical protocols, and as requested by the Study Chair. The Clinical Trials Steering Committee reviews manuscripts based on UCHMC clinical protocols. The timeline for preparing, reviewing, and revising the manuscript will be decided by the Study Chair and the UCHMC Steering Committee on a case-by-case basis.

Publication Acknowledgements

All manuscripts should acknowledge in the title of the paper that the manuscript is a group effort. A suggested mechanism is to follow the title of the paper with the phrase "University of California Hematologic Malignancies Consortium (UCHMC) Study." The manuscript should indicate UCHMC protocol by number.

Authorship
First author will be assigned to the study chair. Senior authorship will be assigned based on contribution to protocol development, not specifically to study enrollment. The order of authorship assignments outside of first and last (senior) author will be based on study enrollment numbers with highest enrolling sites placed earlier in authorship order. Both the local PI and steering committee member, if different, from each site will be included as authors on the publication. References to Patient Data in Publications
In order to ensure that the privacy and confidentiality of UCHMC patients is maintained in publications, measures must be taken to ensure that no personal identifiable data (PID) is released in any publication. When publishing information pertaining to the given patient data and/or samples, investigators are to utilize the study specific ID number.

11.13 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12 REFERENCES

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Appendix A. ECOG Performance Status

ECOG Performance Status Scale	
Grade	Descriptions
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.

Appendix B. FoundationOne™ Heme Sample Requisition Form

FOUNDATIONONE | FOUNDATIONONE Heme

REQUISITION FORM

PLEASE FAX TO: 1 (617)-418-2290
EMAIL: Client.Services@FoundationMedicine.com

*Required Information

Time Sensitive - Please Expedite

☐ First Submission ☐ Second Submission ☐ Associated Requisition _____ ☐ Associated Study _____

Patient Information

Last Name*	First Name*	MI

Patient Medical Record #	Patient DOB*	Patient Gender* ☐M ☐F

Street Address*	Apt. #

City*	State*	Postal Code*	Country

Patient Phone # (Primary)*

Has the patient had any type of transplant?

Ordering Physician Information

Office / Practice / Institution Name*
UCSD Moores Cancer Center

Ordering Physician*	Account #

Street Address*
3855 Health Sciences Drive #0658

City*	State*	Postal Code*	Country
La Jolla	CA	92093	usa

Phone*	Fax*

Email Address*

Pathology Information

Hospital / Institution Name	Submitting Pathologist Name

Phone	Fax

Additional Physician(s) to be Copied

Name

Office/Practice/Facility Name

Phone	Fax

Name

Office/Practice/Facility Name

Phone	Fax

Test Ordered* (CHECK ONE BOX)

☐ FoundationOne™ (Optimized for solid tumors)

☐ FoundationOne™ Heme (Optimized for hematologic malignancies, sarcomas and pediatric cancers)

Full gene lists are available at www.foundationone.com/genelist

Specimen Retrieval

Unless otherwise specified, Foundation Medicine will contact the pathology department indicated above to request your patient's specimen. Please indicate below if you would NOT prefer us to provide this service.

☐ DO NOT contact pathology regarding this case. I will arrange for the specimen to be shipped to Foundation Medicine.

Specimen Information

Diagnosis*	Stage*	Date of Collection*

Specimen Site*	Specimen I.D.*	ICD Code(s) Listed*

Billing Information*

Patient Status** ☐ Hospital Inpatient ☐ Hospital Outpatient ☐ Non-hospital patient
**Must be filled out for Medicare

Institution Name*	Discharge Date

Bill: ☐ Insurance ☐ Medicare - Part B ☐ Hospital/Institution ☐ Self-Pay (*credit card information required)

Primary Insurance	Name on Credit Card

Policy # Group #	Insured Name	Card Holder Address

Patient Relationship to Insured ☐ Self ☐ Spouse ☐ Child ☐ Other	Insured DOB	Credit Card #	Exp. Date

Please Attach the Following

- ☐ Copy of recent pathology/cytology reports
- ☐ Test results from all other Molecular Diagnostic Assays by FISH, IHC, or other genetic assays, e.g. ER, PR, HER2, EGFR KRAS, etc.
- ☐ Front/back copy of insurance card

Comments, Remarks or Special Requests

Certificate of Medical Necessity/Consent

Your signature constitutes a Certificate of Medical Necessity and a certification that you have obtained the patient's consent for Foundation Medicine's release of the test results to the patient's third party payer when necessary as part of the reimbursement process.

Physician Signature*

Ordering Physician Signature*	Date (MM/DD/YYYY)*

Appendix C. MRD Analysis Requisition Form- University of Washington

Specimen #

Patient ID #

Name (Last, First)

D.O.B.

M ☐ F ☐

HEMATOPATHOLOGY

CLINICAL LAB REQUEST

UW MEDICINE

REFERENCE LABORATORY SERVICES

http:// depts.washington.edu/labweb/referencelab/clinical/forms.htm

UW LAB ACC. #	
LOGGED IN BY:	PROCESSED BY:

University of Washington Medical Center
1959 NE Pacific St, NW 220
Seattle, WA, 98195

DATE COLLECTED	TIME COLLECTED

SPECIMEN TYPE
__ Peripheral Blood
__ Bone Marrow Aspirate __ Bone Marrow Biopsy
__ Tissue (site) _____
__ Fresh __ Frozen __ Paraffin embedded
__ Fluid (site) _____
__ BAL __ DNA __ CSF __ Cells
__ Other (specify) _____

ICD9 CODE(S)

ORDERING PHYSICIAN/PROVIDER

CONTACT PHONE #

FAX RESULTS TO

SEND REPORT TO (Hospital, Clinic, Physician)

ADDRESS

CITY STATE ZIP

PATIENT ADDRESS

CITY STATE ZIP

TELEPHONE | PATIENT SOC. SEC. #

SUBSCRIBER NAME

SUBSCRIBER ID. #

GROUP#

Premera Blue Cross Regence DSHS (attach current coupon)

Medicare (answer required question below)

Is this either a hospital outpatient or inpatient?
Yes No
(see reverse for additional information)

OTHER INSURANCE NAME/ADDRESS

REQUIRED

DIAGNOSTIC INFORMATION - Required

B Cell Lymphoma	T Cell Lymphoma	Stem Cell Disorder	Additional Clinical Info:
__ CLL	__ LGL	__ Aplastic Anemia	
__ Follicular	__ Other_____	__ Blast Crisis	
__ Hairy Cell	**Acute Leukemia**	__ CML	
__ Hodgkin's	__ AML	__ MDS	
__ Large Cell	__ B Cell ALL	__ MPN	
__ Mantle Cell	__ T Cell ALL		
__ Myeloma/Gammopathy	__ B/Myeloid		
	__ T/Myeloid		

DISEASE PHASE

___ Presentation ___ MRD/Post Therapy (Days post RX ___) ___ Recurrence

TEST ORDERS - Required

Immunophenotyping
Ph: (206) 288-7060 Fax: (206) 288-7127

Flow Cytometry (Heparin or EDTA)
__ Leukemia/Lymphoma Panel SAVHP
__ If abnormal, archive DNA for future molecular studies. SAVDNA
__ PNH (Paroxysmal Nocturnal Hemoglobinuria) Panel SAVHP

Flow Cytometry (EDTA Only)
__ Hereditary Spherocytosis (Blood Only) FCHS

Lymphocyte Subset Enumeration (Blood Only)
__ T-Cell Subset (CD4, CD8) TCS48
__ T-Cell Subset + CD3 TCSA
__ T-Cell Subset + B & NK Cells TCSNK

Other
Bronchoalveolar Lavage (BAL)
__ Cell Count & Differential SAVHP
__ T-Cell Subset BALTCS
__ Circulating Tumor Cell Assay (CellSave tube only) EPCS
__ Cell Sorting Fractions:_____ SAVHP

Morphologic Evaluation
Ph: (206) 288-7060 Fax: (206) 288-7127

__ Bone Marrow Package (Check items sent)
__ Peripheral Blood (Fresh)
__ Peripheral Blood Smears
__ Bone Marrow Aspirate or Biopsy (Fresh)
__ Bone Marrow Aspirate Smears or Bx TPs
__ Bone Marrow Core Biopsy (Formalin)
__ Bone Marrow Clot/Particle Prep (Formalin)
__ CBC Report

__ Consultation
__ Slides
__ Block(s)
__ Pathology Report

__ Cytologic Exam of CSF CCFUGE
__ Cytologic Exam of Body Fluid FCFUGG
__ Myeloperoxidase Stain MPOB
__ Non-Specific Esterase Stain NSEB

Molecular Studies (EDTA Only) SAVMHP
Ph: (206) 288-7070 Fax: (206) 288-7126

Lymphoma / Multiple Myeloma
__ B-cell clonality (IgH, Kappa)
__ BCL1 t(11;14) (Mantle Cell)
__ BCL2 t(14;18) (Follicular/Large Cell)
__ T-cell clonality (TCR Gamma)

Other Molecular Testing:

Acute Leukemia / Myeloproliferative Disorders
__ NPM1 Insertion Mutations (AML)
__ If neg, reflex to CEBPA
__ CEBPA Mutations (AML)
__ IDH Mutations (AML)
__ KIT D816V Mutation (Mastocytosis/AML)
__ If neg, reflex to KIT Seq.
__ KIT Mutations, DNA Sequencing

__ BCR/ABL, **Qual**itative
__ If pos, reflex to **Quant**itative
__ BCR/ABL, **Quant**itative
Circle One: p190 p210
__ JAK2 V617F Mutation
__ If neg, reflex to MPL
__ MPL Exon 10 Mutations
__ UW-OncoPlex Cancer Gene Panel

UW Cytogenetics and Genomics
Ph: (206) 598-4488 Fax: (206) 598-2610

__ **G-banding Chromosomal Analysis** (Heparin)
__ **Neoplasia IFISH*** (Heparin or FFPE)
*Check Panel; For a complete list of FISH probes go to: www.pathology.washington.edu/clinical/cytogenetics
__ **Oncology Chromosome Microarray Analysis** (EDTA or FFPE)

Neoplasia IFISH Panels
___ AML (M2, M3, M4, M5)
___ AML (M1, M2, M3, M4, M5, inv(3))
___ MDS/MPD (or CMML)
___ B-cell Lymphoma
___ Eosinophilia
___ Multiple Myeloma
___ CLL or SLL
___ T-cell ALL
Other _____

NOTE: When ordering tests for which Medicare reimbursement will be sought, physicians should only order tests which are medically necessary for diagnosis or treatment of the patient. You should be aware that Medicare generally does not cover routine screening tests, and will only pay for tests that are covered by the program and are reasonable and necessary to treat or diagnose the patient.

Revised 09/13

CMS MEDICAL NECESSITY INFORMATION

It is our policy to provide health care providers with the ability to order only those lab tests medically necessary for the individual patient and to ensure that the convenience of ordering standard panels and custom profiles does not impact this ability. While we recognize the value of this convenience, indiscriminate use of panels and profiles can lead to ordering tests that are not medically necessary. Therefore, all tests offered in our panels and profiles can be ordered individually as well. If a component test is not listed individually on the request form, it may be written in the "OTHER REQUESTS" box. We encourage you to order individual tests or a less inclusive profile when not all of the tests included in the panel or profile are medically necessary for the individual patient.

Medicare Billing Information

Medicare billing policy prevents us from submitting a Medicare claim for laboratory testing referred to us on hospital inpatients or hospital outpatients. For these samples, we will bill the sending location.

For outpatient use only: This list has been developed from the most frequently used diagnosis codes and is being provided only as informational assistance in documenting medical necessity. If the correct diagnosis is not found on this list, please furnish the diagnosis by writing text information in the box located in the lower left hand of the front

Code	Description
284.9	Anemia, Aplastic/Refrac Chr
284.89	Anemia, Due to Rx/Rad
280.9	Anemia, Iron Deficiency
281.0	Anemia, Pernicious
285.9	Anemia, Unspecified
283.0	Autoimmune Hemolytic Acq.
284.1	Pancytopenia
282.60	Sickle Cell Disease
282.5	Sickle Cell Trait
282.41	Sickle Cell w/o crisis
282.42	Sickle Cell with crisis
282.49	Thalassemias, other
HEMOSTASIS	
277.30	Amyloidosis, unspecified
444.9	Arterial Emboli/ Thromb.
287.9	Hemorrhage conditions, Unspecified
Factor Deficiencies	
286.0	Factor VIII disorder
286.1	Factor IX disorder
286.2	Factor XI disorder
286.3	Other factor
287.31	Idiopathic Throm Purpura
287.5	Thrombocytopenia, unspec.
289.9	Thrombocytosis
451.9	Thrombophlebitis, unspecified site
MALIGNANT NEOPLASM	
199.1	Malignant neoplasm, other
188.9	Bladder, unspec.
170.9	Bone, unspec.
191.9	Brain, unspec.
174.9	Breast (Female), unspec.
175.9	Breast (Male), unspec.
153.9	Colon, unspec.
150.9	Esophagus, unspec.
150.2	Esophagus, Abdomial Esoph.
195.0	Head, Neck, Face
189.0	Kidney
155.2	Liver, not 1° or 2°
162.9	Lung, unspec.
172.9	Melanoma, unspec.
192.9	Nervous System, unspec.
183.0	Ovary

Code	Description
MALIGNANT NEOPLASM continued	
157.9	Pancreas, unspec.
185	Prostate
173.9	Skin, unspec.
152.9	Small Intestine, unspec.
171.9	Soft Tissue, unspec.
151.9	Stomach, unspec.
186.9	Testes, unspec.
193	Thyroid Gland
_____	Other Specify:_____
PERSONAL HX. NEOP.	
V10.51	Bladder
V10.81	Bone
V10.85	Brain
V10.3	Breast
V10.11	Brochus/Lung
V10.41	Cervix Uteri
V10.00	GI Tract, unspec.
V10.72	Hodgkin's
V10.52	Kidney
V10.62	Leukemia, Myeloid
V10.60	Leukemia, unspecified
V10.61	Leukemia, Lymphoid
V10.71	Non-Hodgkins Lymphoma
V10.82	Melanoma
V10.02	Oral Cavity/Pharynx, other, unspec.
V10.43	Ovary
V10.46	Prostate
V10.47	Testis
V10.12	Trachea
V10.42	Uterus, other
LYMPH/HEMATOPOETIC	
201.40	" Lymph/Histiocytic, unspec.
201.50	" Nodular Sclerosis, unspec.
201.60	" Mixed Cellular, unspec.
201.70	" Lymphocyst Depletion, unspec.
201.90	" Unspecified
202.40	Leukemia, Hairy Cell
204.00	Leukemia, Lymphoid Acute, unspec.
204.10	"Chronic, unspec.
204.80	" Other, unspec.
204.90	" Unspecified

Code	Description
LYMPH/HEMATOPOETIC continued	
203.10	Leukemia, Plasma Cell, unspec.
206.00	Leukemia, Monocytc Acute, no remission
206.10	" Chronic, no remission
206.80	" Other, no remission
206.90	" Unspecified, no remission
205.00	Leukemia, Myeloid Acute
205.10	" Chronic, no remission
205.80	" Other, no remission
205.90	" Unspecified, no remission
238.7	Myelodyplasia Disease
289.8	Myelofibrosis, Myeloid/ Meta
200.20	Lymphoma; Burkitt's, unspec.
200.80	Lymphosarcoma,Cleaved/Other, unspec.
200.80	Lymphosarcoma,Mixed, unspec.
200.00	Reticulosarcoma, Large Cell, unspec.
200.10	Lymphosarcoma, Lymphoblastic, unspec.
202.00	Lymphoma; Follicular, unspec.
202.60	Mast Cell Tumors, unspec.
202.10	Mycosis Fungoides, unspec.
205.30	Myeloid Sarcoma, no remission
203.00	Myeloma, Multiple, no remission
202.20	Sezary's Disease, unspec.
METASTATIC NEOPLASM	
198.3	Brain/ Spinal Cord
197.0	Lung
197.7	Liver, secondary
196.9	Lymph Nodes, Unspec.
198.6	Ovary
_____	Other Specify:_____
MISCELLANEOUS	
780.6	Fever
279.00	Hypogammaglobulinemia, unspec.
075	Infectious Mononucleosis
288.0	Leukopenia/Agranulocytosis
238.7	Lymphoproliferative, chronic, unspec.
273.3	Macroglobulinemia
273.1	Monoclon. Gammopath (B)
340	Multiple Sclerosis
273.2	Paraproteinemias, other
486	Pneumonia, unspec.
238.4	Polycytemia vera

Appendix D: UCHMC1504 Eligibility Criteria Checklist

Study Title: "A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast percentage: University of California Hematologic Malignancies Consortium Study #1504 (UCHMC1504)"

Patient Initials:_____ SID: 1504-____-____-____
DOB:_____

Inclusion Criteria		Yes	No
1	Ability to understand and the willingness to sign a written informed consent.		
2	Relapsed or refractory CD19-positive B-lineage acute lymphoblastic leukemia having received at least 1 prior line of therapy		
3	Philadelphia chromosome/BCR-ABL1-positive B-lineage ALL must have failed at least 1 second or third generationTKI or be intolerant to TKIs		
4	Greater than 50% lymphoblasts on screening bone marrow aspirate or biopsy		
5	Evidence of CD19 expression via flow cytometry (peripheral blood or bone marrow) or immunohistochemistry (bone marrow biopsy) from a sample obtained from the current relapse		
6	Adults 18 years of age or older		
7	ECOG performance status 0 or 1		
8	Adequate organ function defined as: ☐ Bilirubin <1.5x upper limit of normal (ULN) unless believed due to leukemic infiltration ☐ AST or ALT ≤2.5x ULN unless believed due to leukemic infiltration creatinine clearance ≥60 mL/min/1.73 m^2 unless reduced creatinine clearance felt by investigator to be acute and reversible		
9	Women of child-bearing potential and men with partners of child-bearing potential must agree to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. • A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: ☐ Has not undergone a hysterectomy or bilateral oophorectomy; or ☐ Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months)		
10	Women of childbearing potential has negative pregnancy test within 72 hours of initiating study drug dosing		
11	Male subjects must agree to use a latex condom during sexual contact with females of child bearing potential even if they have had a successful vasectomy starting with the first dose of study therapy through 120 after the last dose of study therapy.		
12	Corticosteroids and hydroxyurea are permitted after screening bone marrow biopsy is performed and for up to 7 days prior to starting study therapy		

Exclusion Criteria	Yes	No

1	Allogeneic HSCT within 5 years of study drug administration		
2	Current or anticipated use of other investigational agents during the study		
3	GM-CSF or GCSF use within 2 weeks of study treatment and throughout the study		
4	Clinical Evidence of active CNS or testicular involvement by leukemia		
5	Active second malignancy excluding non-melanoma skin cancer		
6	Burkitt Lymphoma/Leukemia		
7	Diagnosis of congenital immunodeficiency		
8	Known history of active TB		
9	Known HIV infection		
10	Active Hepatitis B or Hepatitis C infection		
11	Any uncontrolled infection		
12	Has received a live vaccine within 30 days prior to first dose		
13	Prior checkpoint inhibitor therapy including anti-PD-1, anti-PD-L1, anti-CTLA4, anti-CD37 or anti-PD-L2 therapy		
14	Prior treatment with any CD19-directed therapy (e.g. blinatumomab, CD19-directed chimeric antigen receptor T-cell therapy, anti-CD19 antibodies).		
15	Pregnant or breastfeeding		
16	History of autoimmune disease		
17	Known interstitial lung disease		
18	Active, non-infectious pneumonitis or has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis		
19	Patients who have received chemotherapy or radiotherapy within 2 weeks prior to entering the study or has not recovered from adverse events due to agents administered more than 2 weeks earlier.		
20	Patients who are less than 4 weeks from surgery or have insufficient recovery from surgical-related trauma or wound healing		
21	History of allergic reactions attributed to compounds of similar chemical or biologic composition to blinatumomab or pembrolizumab or other agents used in study		
22	Impaired cardiac function as specified in the protocol		
23	Any condition that requires the use of corticosteroids outside of corticosteroids defined in the protocol after Day 1 of therapy with the exception of topical or inhaled steroids.		
24	Severe or uncontrolled medical disorder that would, in the investigator's opinion, impair ability to receive study treatment (i.e., uncontrolled diabetes, chronic renal disease, chronic pulmonary disease or active, uncontrolled infection, psychiatric illness/social situations that would limit compliance with study requirements)		

Investigator/Sub-Investigator Signature Date

With eligibility checklist please provide the below items in order to confirm eligibility:

1. Signed Informed Consent
2. All source (redacted with patient initials and DOB) required to confirm eligibility, including but not limited to
    a. Bone Marrow biopsy
    b. Physical exam with vitals, ECOG, and medical history
    c. Lab results
    d. Confirmation of foundation one submission

Please email via secure email to JReiner@ucsd.edu and MWieduwilt@ucsd.edu

Upon confirmation of eligibility by initiating site within 24-48 hours of receiving, patient study ID will be provided and patient may initiate treatment

Appendix E. Statement of Planned Allogeneic HCT

Protocol ID: UCHMC1504
Study Title: "A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast percentage:University of California Hematologic Malignancies Consortium Study #1504 (UCHMC1504)"

Patient Initials:_____ SID: 1504-____-_____.

DOB:_____

☐ At this time, there is no intent for the patient to ultimately receive allogeneic transplant.

☐ At this time, the intent is for the patient to ultimately receive an allogeneic transplant.

_____

Investigator/Sub-Investigator Signature Date

Please fax to Jesika Reiner at 858-822-1473 or email via secure email to JReiner@ucsd.edu upon completion along with eligibility checklist and signed informed consent.

Appendix F. Correlative Research Sample Requisition Form

UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER

Clinical Trials Office
3855 Health Sciences Drive, #0698
La Jolla, CA 92093-0698
Phone (858) 822-5367
Fax (858) 822-5380

Sample Collection Case Report Form

Lymphoblast PD-L1 and PD-L2 expression by Western Blot

UCHMC#	UCHMC1504	**UCSD Investigator Name:**	Matthew Wieduwilt, MD, PhD
Site:		**Site #:**	
Protocol Title:	A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast percentage: University of California Hematologic Malignancies Consortium Study #1504 (UCHMC1504)		

Study ID	
DOB	
Date Collected	
Time Collected	

Time Point	☐ Screening ☐ Cycle 1 Day 14 ☐ Cycle 1 Day 29+8

Email the completed sample collection form prior to shipment to: **JReiner@ucsd.edu**

Make a copy of the form to include with the sample(s)

Retain the original at the site for your records

Email a de-identified (redacted) pathology report(s) if available. Write the Study ID on the top of each page of the pathology report.

3-5 mL of bone marrow aspirate to be collected in EDTA (lavender-top) tube and shipped ambient overnight:

Gerald Morris, MD, PhD
Department of Pathology
University of California San Diego
249A Leichtag Family Foundation Biomedical Research Building
9500 Gilman Drive
La Jolla, CA 92093
Ph: 858-822-3490
Email: gpmorris@ucsd.edu

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UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER

Clinical Trials Office
3855 Health Sciences Drive, #0698
La Jolla, CA 92093-0698
Phone (858) 822-5367
Fax (858) 822-5380

Sample Collection Case Report Form

T-cell subsets, PD-1 and PD-L1 expression studies by Flow Cytometry

UCHMC#	UCHMC1504	**UCSD Investigator Name:**	Matthew Wieduwilt, MD, PhD
Site:		**Site #:**	
Protocol Title:	A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast percentage: University of California Hematologic Malignancies Consortium Study #1504 (UCHMC1504)		

Study ID	
DOB	
Date Collected	
Time Collected	

Time Point	☐ Screening ☐ Cycle 1 Day 14 ☐ Cycle 1 Day 29+8 ☐ Cycle 2 Day 29+8

Email the completed sample collection form prior to shipment to: **JReiner@ucsd.edu**

Make a copy of the form to include with the sample(s)

Retain the original at the site for your records

Email a de-identified (redacted) pathology report(s) if available. Write the Study ID on the top of each page of the pathology report.

3-5 mL of bone marrow aspirate to be collected in EDTA (lavender-top) tube and shipped ambient overnight:

Gerald Morris, MD, PhD
Department of Pathology
University of California San Diego 249A Leichtag Family Foundation Biomedical Research Building
9500 Gilman Drive
La Jolla, CA 92093
Ph: 858-822-3490
Email: gpmorris@ucsd.edu

UNIVERSITY of CALIFORNIA, SAN DIEGO
MEDICAL CENTER MOORES CANCER CENTER

Clinical Trials Office
3855 Health Sciences Drive, #0698
La Jolla, CA 92093-0698
Phone (858) 822-5367
Fax (858) 822-5380

Sample Collection Case Report Form

Serum cytokine assays

UCHMC#	UCHMC1504	**UCSD Investigator Name:**	Matthew Wieduwilt, MD, PhD
Site:		**Site #:**	
Protocol Title:	A Phase I/II study of blinatumomab in combination with pembrolizumab (MK-3475) for adults with relapsed or refractory B-lineage acute lymphoblastic leukemia with high bone marrow lymphoblast percentage: University of California Hematologic Malignancies Consortium Study #1504 (UCHMC1504)		

Study ID	
DOB	
Date Collected	

Time Collected	
Study Day	

Email the completed sample collection form prior to shipment to: **JReiner@ucsd.edu**

Make a copy of the form to include with the sample(s)

Retain the original at the site for your records.

Peripheral blood to be collected in 1-10mL EDTA tube.
Sample to be processed at 1200g for 10min and the plasma stored at -70C.

Samples to be batched and shipped overnight on dry ice:

Study Coordinator, BMT Clinical Trials
UCSD Moores Cancer Center
3855 Health Sciences Drive, Room 2037
La Jolla, CA 92093
Tel: 858-822-5364/6396/6397

Appendix G. Pembrolizumab Program: Events of Clinical Interest

PEMBROLIZUMAB PROGRAM
(MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

REVISION HISTORY LOG

Version	Effective Date[a]	Revision Author	Action
1	08-Aug-2012	Kevin Gergich	Initial Release of guidance document for MK-3475
2	07-June-2013	Marty Huber, Kevin Gergich, Holly Brown	Revised title, formerly was "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance Document for Investigators" Revised the format of irAE Guidance document, including layout, font, sectioning, etc. for consistency with Sponsor Events of Clinical Interest guidance documents. Modified Categories for irAEs: – Replaced GI with Colitis category. – Removed Neurologic category. – Added Renal category. Removed detail in the irAE Guidance document that can be located in the Investigator's Brochure for MK-3475. Removed details regarding non-MK-3475 compounds. Added ECI reporting guidelines. Included a Table Events of Clinical Interest: Immune-Related Adverse Events that includes the key terms. – Also placed a pull-out quick-review sheet in the Appendix. Updated background, diagnosis and course of treatment details for irAEs.
3	10-Sep-2014	Marty Huber, Kevin Gergich, Holly Brown	Renamed the document: "Pembrolizumab Program (MK-3475) - Events of Clinical Interest Guidance Document". Introduced generic name: pembrolizumab (MK-3475) and inserted throughout the document. Updated Overview – Section 1 - Clarified the scope of the document and the reporting window for ECIs - Updated Table 1 with medDRA Preferred Terms for adverse events to correspond with reporting of terms to clinical database, rearranged the order, and updated the reporting criteria. - Updated the dose modification/discontinuation section to clarify discontinuation and hold terminology. Updated Section 2 – ECI Reporting Guidelines

			– Clarified that ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment or etiology. Updated Section 3 – For All Sections, removed the Course of Action for Grade 1 events. - Section 3.1 Pneumonitis – Moved Pneumonitis to beginning of ECI Section – Updated management guidelines for Grade 2 and Grade 3-4 events - Section 3.2 Colitis: - Updated AE terms and ECI criteria, updated course of action language for clarity - Section 3.3 Endocrine: - Updated ECI criteria and updated course of action language for clarity. - Added subsections for hypophysitis, hyperthyroidism and hypothyroidism to clarify management guidelines. - Section 3.4 Hematologic: - New section added. - Section 3.5: Hepatic: - Updated terms and added additional guidance for reporting of DILI ECI; updated course of action for clarity - Section 3.6 Neurologic: - New section added. - Section 3.7 Ocular: - Changed the name of this section from Eye to Ocular - Added the term "iritis", updated ECI guidance, and updated course of action language for clarity - Section 3.8 Renal: - Updated section for clarity. - Section 3.9 Skin: - Updated list of terms and added terms for reporting of other skin ECIs; added section 3.9.1: Immediate Evaluation for Potential Skin ECIs - Section 3.10 Other: - Updated list of terms for clarity; revised course of action for clarity.

			- Section 3.11 Infusion Reactions: - New section added. - Section 3.12: Follow-up to Resolution: - New section added. - Section 4: - References updated. - Section 5: - ECI table updated for consistency with Table 1. - Section 6: Appendix 2 – Past Medical History Related to Dermatologic Event: New section added. - Section 7: Appendix 3 – Presentation of the Dermatologic Event: New section added. - Section 8: Appendix 4 – Focused Skin Examination: New section added.
4	04-Dec-2014	Scot Ebbinghaus, Oswaldo Bracco, Holly Brown, Kevin Gergich	- Table 1 - Updated Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE) Section to include: - Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA) - Created new section in Table 1 – Endocrine (reported as ECI) and added: - Type 1 diabetes mellitus (if new onset) - Hepatic: Clarified Transaminase elevations as: - Transaminase elevations (ALT and/or AST) - Section 3.2 Colitis - Updated the duration of diarrhea requirments under the Course of Action for Grade 2 and Grade 3 - Section 3.3 Endocrine - Clarified Course of Action for hyperthyroidism and hypothyroidism - Added Course of Action section for Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 hyperglycemia - Section 5 - Updated Reference Table in Appendix 1
5	18-Dec-2014	Holly Brown Kevin Gergich	- Section 3.3 Endocrine - Updated the Course of Action for Hypophysitis - Merged Grades 2-4 into one course of action

*Ensure that you are using the most current version of this document.

TABLE OF CONTENTS

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 1: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Sponsor contact.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

- Please refer to the Data Entry Guidelines (DEGs) for your protocol.
- Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection. **It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,
  - Consider GI consultation and endoscopy to confirm or rule out colitis
  - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

- Report as ECI
- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

3.3 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Adrenal insufficiency
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder
- Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-4 events:

- Report as ECI if appropriate
- Hold pembrolizumab
- Rule out infection and sepsis with appropriate cultures and imaging.
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Consultation with an endocrinologist may be considered.

Hyperthyroidism and Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor patients 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.

Grade 2 hyperthyroidism, Grade 2-4 hypothyroidism events:

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 hyperthyroidism events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
- Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of pre-existing diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:

- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hemolytic anemia
- Aplastic anemia
- Disseminated Intravascular Coagulation (DIC)
- Haemolytic Uraemic Syndrome (HUS)
- Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
  Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
- Report as ECI
- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Report as ECI
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

- Report as ECI
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre syndrome
- Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

- Report as ECI
- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.7 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:
- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:

- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:
- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9.1. Immediate Evaluation for Potential Skin ECIs

A. Photographs:
Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible. **Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.
- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:
Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:
Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:
Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult
Refer the subject to a dermatologist as soon as possible.

- For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:
- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:
- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

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 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 p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (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., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine 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. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
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 v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

4. REFERENCES

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5. APPENDIX 1 –Events of Clinical Interest (ECI) – Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficieney	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

6. APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc):
_____
_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____
_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____
_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

7. APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?
_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No