To: CTEP Protocol and Information Office

From: Erel Joffe, MD

Date: May 21, 2020

Re: Amendment 18

SUMMARY OF CHANGES – Protocol

I. PIO Recommendations:

#	Section	Comments
1.	8.1.1	The MK-3475 (pembrolizumab) vial equilibration to room temperature is no longer required by the pharmaceutical collaborator and can be removed from the preparation instructions. "**Preparation:** MK-3475 solution for infusion must be diluted prior to administration. ~~Allow the required number of vials to equilibrate to room temperature.~~ Do not shake the vials." **PI Response:** This sentence was removed.
2.	8.1.1	The MK-3475 (pembrolizumab) infusion solution stability is updated per the current Investigator Brochure with refrigerated temperature allowance from 20 hours to 24 hours and room temperature allowance from 4 hours to 6 hours. Please update accordingly. "**Stability:** Stability testing of the intact vials is on-going**.** Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 6 hours." **PI Response:** These times were updated.

II. PI Requested Changes

#	Section	Comments
1.	**All**	General formatting throughout the document.
2.	Cover Page	Changed the Protocol Contact's information.
3.	Schema 5.1	Added the following statement: "As of 08/10/2019, we are using dose level (-1) due to limited feasibility of administering dose level 1." In the corresponding table, Dose Level 1 was retained but crossed out.
4.	2.1	Clarified the study is for relapsed or refractory patients with *DLBCL*.
5.	3.1.5	Changed the eligibility Performance Status criteria to ECOG ≥ 1 (Karnofsky ≥ 80 %).
6.	3.1.10	Corrected section numbering 3.1.11 to 3.1.10.
7.	3.2.1	Revised prior systemic anti-cancer therapy washout from 3 weeks to 2 weeks or 5 half lives (the shorter of the two).
8.	5.2	Removed the first DLT (Grade 4 nonhematologic toxicity (not laboratory)). Renumbered subsequent items.
9.	5.3	Under *Prohibited Concomitant Medications*, removed the statement in parentheses and added information pertaining to radiation therapy.
10.	5.6	Removed the section *Criteria to Resume Treatment* in its entirety and renumbered the subsequent sections.
11.	5.9	Revised the maximum number of cycles of mogamulizumab from 35 to 34.
12.	10	Calendar: Added +/- 2 days windows to the study calendar. Footnote c: Clarified EKGs are every 3 weeks from C4 onward. Footnote j: Added timeframe for the Off Treatment visit.

SUMMARY OF CHANGES – Consents

I. Phase 1

#	Section	Comments
1.	Header	Protocol version date revised.

II. Phase 2

#	Section	Comments
1.	Header	Protocol version date revised.

NCI Protocol #: 10106
Protocol Version Date: 05/21/2020

Local Protocol #: 19-018

ClinicalTrials.gov Identifier: NCT03309878

TITLE: A phase I and randomized phase II study of KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab) in relapsed, refractory diffuse large-B cell lymphoma

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NCI-Supplied Agents: MK-3475 (pembrolizumab) (NSC 776864)
KW-0761 (mogamulizumab) (NSC 791064

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Original / Version 1 / 8/14/2017
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Revised / Version 5 / 03/12/2018
Revised / Version 6 / 03/27/2018
Revised / Version 7 / 04/10/2018
Revised / Version 8 / 04/23/2018
Revised / Version 9 / 05/15/2018
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Revised / Version 17 / 03/10/2020
Revised / Version 18 / 05/21/2020

SCHEMA

There are two parts to this study. The first part is a phase I, multicenter, open-label study designed to evaluate the safety and tolerability of KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) in patients with relapsed, refractory diffuse large B-cell lymphoma. A traditional 3+3 phase I design on sequential dosing cohorts will be applied. MK-3475 (pembrolizumab) will be given at a dose of 200mg IV on day 1 of every 21-day cycle. KW-0761 (mogamulizumab) will be administered at the doses specified in Table 1. The starting dose level for the Phase I is Level 1 (see Table 1).

Table 1.
As of 08/10/2019, we are using dose level (-1) due to limited feasibility of administering dose level 1.

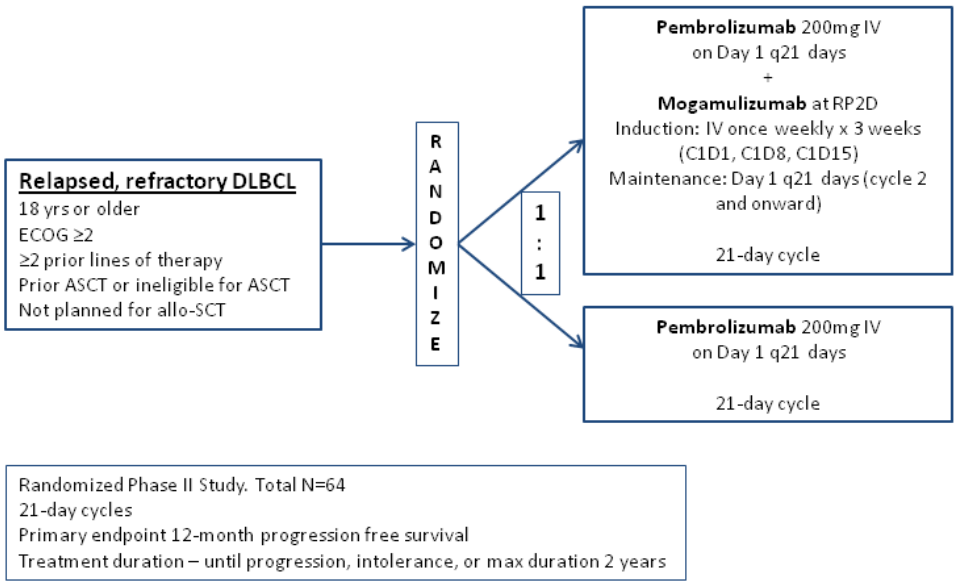
Dose Escalation Schedule		
Dose Level	**Dose**	
	MK-3475 [Pembrolizumab] (mg)	**KW-0761 [Mogamulizumab] (mg/kg)**
Level -1	200mg IV day 1 every 21 days	Induction: 0.5 mg/kg IV weekly for 3 weeks Maintenance: 1mg/kg IV day 1 every 21 days
~~Level 1~~	~~200mg IV day 1 every 21 days~~	~~Induction: 1 mg/kg IV once weekly for 3 weeks~~ ~~Maintenance: 1.5mg/kg IV day 1 every 21 days~~

The primary objective of this part of the study is to determine the maximum tolerated dose (MTD) or recommended phase II dose (RP2D) of KW-0761 (mogamulizumab) in combination with MK-3475 (pembrolizumab) and characterize the safety and toxicity profile of the combination. The maximum treatment duration for the phase I part of the study is 2 years.

The second part of this study is a phase II, randomized, multi-center, open-label study designed to evaluate the efficacy of the combination of MK-3475 (pembrolizumab) and KW-0761 (mogamulizumab) versus single-agent MK-3475 (pembrolizumab) (see Figure 1). In the phase II portion of the study, patients with relapsed, refractory diffuse large B-cell lymphoma will be treated. Patients will be randomly assigned, in a 1:1 ratio, to receive either MK-3475 (pembrolizumab) and KW-0761 (mogamulizumab) in combination versus MK-3475 (pembrolizumab) alone. In other words, there will be two treatment groups: Group 1 (MK-3475 [pembrolizumab] and KW-0761 [mogamulizumab]) and Group 2 (MK-3475 [pembrolizumab] alone). Patients will receive either MK-3475 (pembrolizumab) 200mg IV on day 1 of every 21-day cycle and KW-0761 (mogamulizumab) at the induction RP2D once weekly for 3 weeks (C1D1, C1D8, C1D15) and thereafter at the maintenance RP2D on day 1 of every 21-day cycle (C2D1, C3D1, etc) (Group 1) or MK-3475 (pembrolizumab) alone (Group 2). MK-3475 (pembrolizumab) will be administered in both arms at a dose of 200mg IV on day 1 of every 21-

day cycle. The primary endpoint for the phase II portion is progression free survival.

Figure 1



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1. OBJECTIVES

1.1 Primary Objectives

The primary objectives of the Phase I portion of the study are the following:

1.1.1 To determine the MTD or RP2D of KW-0761 (mogamulizumab) when administered in combination with MK-3475 (pembrolizumab) in patients with relapsed, refractory diffuse large B-cell lymphoma.

1.1.2 To assess the safety and tolerability of KW-0761 (mogamulizumab) when administered in combination with MK-3475 (pembrolizumab) in patients with relapsed, refractory diffuse large B-cell lymphoma.

The primary objective of the Phase II portion of the study is the following:

1.1.3 To assess the progression-free survival of KW-0761 (mogamulizumab) when administered in combination with MK-3475 (pembrolizumab) compared to MK-3475 (pembrolizumab) alone in patients with relapsed and refractory diffuse large B-cell lymphomas.

1.2 Secondary Objectives

The secondary objective of the Phase I portion of the study is the following:

1.2.1 To observe and record anti-tumor activity. Although the clinical benefit of this drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

The secondary objective of the Phase II portion of the study is the following:

1.2.2 To assess the overall response rate, complete response rate, partial response rate, duration of response of KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) compared to MK-3475 (pembrolizumab) alone in patients with relapsed and refractory diffuse large B-cell lymphomas.

1.3 Exploratory Objectives

1.3.1 To determine whether the progression-free survival of KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) when administered to patients with relapsed and refractory diffuse large B-cell lymphomas differs based on the presence or absence of mutations in B2M or CD58 or amplifications in PD-L1.

1.3.2 To determine whether the progression-free survival of KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) when administered to patients with relapsed and refractory diffuse large B-cell lymphomas differs based on changes in CD8 T-cell, NK cell, and FoxP3+ Treg prevalence in response to therapy as measured by immunohistochemistry

1.3.3 To determine whether KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) alters the prevalence of peripheral blood CCR4+/FoxP3+ regulatory T-cells as well as effector CD4 and CD8 T-cells by multi-parametric flow cytometry

2. BACKGROUND

2.1 Study Disease

The phase I portion of the study will be open to patients with relapsed or refractory DLBCL. Patients with these diseases who experience a relapse after more than one line of treatment or after autologous stem cell transplant generally have poor outcomes. Evasion of the immune system through various mechanisms has been shown to be an important part of lymphoma pathogenesis and immune blockade of the PD-1/PD-L1 interaction with monoclonal antibodies to augment antitumor activity has shown therapeutic promise in many subtypes of lymphoma (Ansell et al., 2015; Lesokhin et al., 2016).

Diffuse large B-cell lymphoma (DLBCL) represents a unique and ongoing therapeutic challenge in clinical oncology. Only about half of patients are cured with standard chemotherapy-based approaches. For relapsed patients, curative therapy requires autologous or allogeneic transplant, which carries a high risk of treatment-related morbidity and maybe inappropriate for elderly or comorbid patients. Additionally, a significant proportion of patients experience disease relapse following transplant, at which point therapeutic options are limited and conventional chemotherapeutic agents show limited activity and duration of response. This underscores the need for well-tolerated targeted therapies that can promote long-lasting remissions.

2.2 CTEP IND Agents

2.2.1 MK-3475 (Pembrolizumab)

MK-3475 (pembrolizumab) has high affinity and potent receptor-blocking activity for the programmed cell death 1 (PD-1) receptor, based on preclinical in vitro data (Investigator's Brochure, 2016). MK-3475 (pembrolizumab) has an acceptable preclinical safety profile and is being advanced for clinical development as an intravenous (IV) immunotherapy for advanced malignancies. The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis et al., 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma (Dudley et al., 2005; Hunder et al., 2008).
The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (programmed cell death ligand 1 [PD-L1] and/or programmed cell death ligand 2 [PD-L2]) (Greenwald et al., 2005; Okazaki et al., 2001).

The structure of murine PD-1 has been resolved (Zhang et al., 2004). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP 1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009). The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (Parry et al., 2005; Francisco, 2010).

2.2.2 MK-3475 (pembrolizumab) Background and Clinical Trials

MK-3475 (pembrolizumab, Keytruda®), a humanized monoclonal antibody against the PD-1 protein, has been developed by Merck & Co. for the treatment of cancer. MK-3475 (pembrolizumab) is approved for treatment of melanoma in several countries; in the United States (US) and European Union it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. MK-3475 (pembrolizumab) has also been approved for treatment of NSCLC in several countries; in the US it is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA)-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with NSCLC and epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should also have disease progression on FDA-approved therapy for these aberrations prior to receiving MK-3475 (pembrolizumab). MK-3475 (pembrolizumab) is approved in the US for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.

MK-3475 (pembrolizumab) has demonstrated initial clinical efficacy in single-arm monotherapy trials in patients with NSCLC, HNSCC, urothelial cancer, gastric cancer, triple negative breast cancer, and Hodgkin's Lymphoma as determined by response rate. Ongoing clinical trials are being conducted in these tumor types as well as a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the Investigator's Brochure (2016).

2.2.3 Rationale for MK-3475 (pembrolizumab) Dose Selection

The dose of MK-3475 (pembrolizumab) planned to be studied in this trial is 200 mg administered IV every 3 weeks (Q3W). The dose recently approved in the US and several other countries for treatment of melanoma patients is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

The initial phase 1 study of MK-3475 (pembrolizumab) evaluated 5 dose levels (1 mg/kg every 2

weeks [Q2W], 3 mg/kg Q2W, 10 mg/kg Q2W, 2 mg/kg Q3W, and 10 mg/kg Q3W) in patients with advanced solid tumors. All 5 dose levels were well tolerated and no dose-limiting toxicities (DLTs) were observed. MK-3475 (pembrolizumab) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. In addition, 2 randomized cohort evaluations of melanoma patients receiving MK-3475 (pembrolizumab) 2 mg/kg or 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W or 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of any important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat MK-3475 (pembrolizumab) exposure-response relationship for efficacy and safety has been found in patients with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

The PK profile of MK-3475 (pembrolizumab) is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. The PK properties of MK-3475 (pembrolizumab), specifically the weight-dependency in clearance and volume of distribution, are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in patients with melanoma can be expected. As the antitumor effect of MK-3475 (pembrolizumab) is driven through immune system activation rather than through a direct interaction with tumor cells, it is rendered independent of the specific tumor type. In addition, available PK results in patients with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses across tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.
A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for MK-3475 (pembrolizumab).

2.2.4 Summary of safety

MK-3475 (pembrolizumab) has a positive benefit-risk profile and is well tolerated in the approved indications, as evidenced by a low rate of toxicity Grade 3 to 5 drug-related AEs (13.8%), discontinuations due to AEs (11.9%), and deaths due to drug-related AEs (0.4%). Furthermore, the frequency of immune-mediated AEOSIs is low, and these events are readily managed in the

clinical setting with widely available set of guidelines. The safety and efficacy data generated to date provide a favorable benefit-risk assessment for the use of MK-3475 (pembrolizumab) as a treatment for subjects with advanced/metastatic melanoma, NSCLC, and HNSCC (Investigator's Brochure, 2017).

2.2.5 KW-0761 (Mogamulizumab)

KW-0761 (also known as AMG 761, mogamulizumab, and POTELIGEO®) is a recombinant, humanized monoclonal antibody (mAb) of the immunoglobulin (Ig) G subclass 1 kappa (IgG1κ) isotype that targets CC chemokine receptor 4 (CCR4)-expressing cells that is being developed by Kyowa Kirin Pharmaceutical Development, Inc. (KKD) for the treatment of T-cell malignancies including peripheral T-cell lymphoma (PTCL), cutaneous T-cell lymphoma (CTCL), and adult T-cell leukemia-lymphoma (ATL), and solid tumors (Investigator's Brochure, 2016).

KW-0761 (mogamulizumab) was produced using technology developed by Kyowa Hakko Kirin Co., Ltd. (KHK, the parent company of KKD), that eliminates fucose from the carbohydrate structure of the antibody. Due to the absence of fucose from the complex-type oligosaccharide at the constant (fragment crystallizable) region, KW-0761 (mogamulizumab) has enhanced antibody-dependent cellular cytotoxicity (ADCC) activity, but does not exhibit any complement dependent cytotoxic (CDC) activity or neutralizing activity of the ligand of CCR4.

KW-0761 (mogamulizumab), which eliminates CCR4+ cells, has induced anti-tumor responses in patients with CCR4+ T-cell malignancies, which is thought to be due to ADCC-mediated killing of CCR4+ malignant cells (Ishida et al., 2012). KW-0761 (mogamulizumab) has also been shown to deplete a subset of T regulatory cells (Tregs) which expresses CCR4. Sugiyama *et al.* showed that CCR4 was specifically expressed by a subset of terminally differentiated highly suppressive CD45RA-FOXP3hiCD4+ Tregs but not by CD45RA+FOXP3lowCD4+ naive Treg cells in the peripheral blood of healthy individuals and cancer patients (Sugiyama et al., 2013). They showed that KW-0761 (mogamulizumab) produced a substantial reduction in the number of circulating Tregs in a patient with ATL. In addition, peripheral blood mononuclear cells (PBMCs) were collected from patients with melanoma whose tumors expressed the NY-ESO-1 antigen, but in whom there was no evidence of an immune response against this antigen. When these PBMCs were cultured in the presence of the NY-ESO-1 antigen and with an antibody to CCR4 to deplete the CCR4+ cells, the remaining CD4+ cells activated to secrete interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). This indicated that the immunosuppressive influence of Treg cells had been removed by removing cells expressing CCR4 (Sugiyama et al., 2013; Kurose et al., 2015).

Additional evidence for the role of KW-0761 (mogamulizumab) in depleting Tregs is provided by the results of a Phase 2 study in subjects with relapsed ATL, which demonstrated that a single treatment course with KW-0761 (mogamulizumab) (8 doses of 1 mg/kg given once weekly) resulted in a marked decrease in CD4+CD25+FoxP3+ cells after the first dose, which persisted for at least 4 months after the last dose of KW-0761 (mogamulizumab) (Ishida et al., 2012).

KW-0761 (mogamulizumab) has been examined for safety and toxicology in non-human primates with little toxicity. The No Observed Adverse Effect Level (NOAEL) in a 26-week repeat-dose

toxicology study conducted in cynomolgus monkeys was 40 mg/kg, the highest dose evaluated. Additionally, an embryo-fetal development study performed in cynomolgus monkeys demonstrated that the NOAEL for general toxicity and reproductive function in dams was 40 mg/kg.

In human clinical trials, doses of up to 1.0 mg/kg have been well tolerated. As of 30 Sep 2016, more than 800 subjects have received at least one dose of KW-0761 (mogamulizumab) in company-sponsored clinical studies.

POTELIGEO® (mogamulizumab) was approved by the Ministry of Health, Labor and Welfare in Japan for the treatment of primary (14 Dec 2014) and relapsed or refractory CCR4+ ATL (30 Mar 2012), relapsed or refractory CCR4+ PTCL (17 Mar 2014), and relapsed or refractory CCR4+ CTCL (17 Mar 2014).

2.2.6 Summary of nonclinical pharmacology

Nonclinical pharmacological studies designed to examine the anti-tumor activity of KW-0761 (mogamulizumab) identified: (1) the binding of KW-0761 (mogamulizumab) to CCR4 peptide, FcγRIIIa (F) and FcγRIIIa (V); (2) the binding of KW-0761 (mogamulizumab) to T-cell lymphoma cell lines (3) the in vitro ADCC activity to T-cell lymphoma/leukemia cell lines and tumor cells from ATL and PTCL-NOS patient; and (4) the in vivo effects of KW-0761 (mogamulizumab) to ATL and CTCL cell lines in a SCID mouse model. These results demonstrated that KW-0761 (mogamulizumab) exhibited potent ADCC activity against CCR4-expressing lymphoma cell lines in vitro and exerted anti-tumor activity in vivo against T-cell lymphoma making KW-0761 (mogamulizumab) a promising candidate for a single agent treatment for T-cell lymphomas.

Other characteristics are summarized as below:

- KW-0761 (mogamulizumab) induced reduction of CCR4+ cells, including Treg cells, in peripheral blood of cynomolgus monkeys.
- KW-0761 (mogamulizumab) neither affected the binding of CCR4 ligands (TARC or MDC) to CCR4 nor the viability of CCR4-expressing human cutaneous T cell lymphoma HuT78 cells.
- KW-0761 (mogamulizumab) binding had little effect on the level of CCR4 expression on the CTCL surface.
- KW-0761 (mogamulizumab) exhibited no CDC activity against human T-cell leukemia and lymphoma cell lines.

KW-0761 (mogamulizumab) did not bind to platelets and had no effect on platelet aggregation or on reduction of platelet counts in the whole blood. KW-0761 (mogamulizumab) induced TNF-α, IFN-γ, and IL-6 release from human whole blood and PBMCs.

2.2.7 Summary of nonclinical pharmacokinetics

Absorption
Pharmacokinetic analysis of plasma KW-0761 (mogamulizumab) concentration profiles following

a single intravenous dose to male and female cynomolgus monkeys was conducted at doses between 0.01 and 100 mg/kg. Plasma KW-0761 (mogamulizumab) concentration decreased biphasically after an iv administration in the 0.01 to 100 mg/kg dose groups. Pharmacokinetic parameters were calculated with a two-compartment open model. Pharmacokinetic parameters were similar among groups dosed from 0.5 to 100 mg/kg, with average elimination half-lives (t1/2β) of 13.9 to 20.8 days. The volume of distribution at steady-state of KW-0761 (mogamulizumab) for all groups almost corresponded to the plasma volume of monkeys (approximately 45 mL/kg). The plasma KW-0761 (mogamulizumab) concentration decreased rapidly in the monkeys that generated anti-KW-0761 (mogamulizumab) antibodies.

The area under the concentration-time curves (AUCs) was approximately dose-proportional between the 1.2 mg/kg and 40 mg/kg doses. Compared with t1/2β at 40 mg/kg, the t1/2β at 0.05 mg/kg was significantly shorter. No sex-related differences in the pharmacokinetic parameters of KW-0761 (mogamulizumab) were observed at either dose level were apparent.

The accumulation ratios (Cmin, Day 28/Cmin, Day 8) were 2.04 to 3.12 following repeated administration in the 1.2 and 40 mg/kg dose groups and were approximately consistent with those predicted from the t1/2β value.

At 0.05 mg/kg, the plasma KW-0761 (mogamulizumab) concentration after repeated doses rapidly decreased when compared with those after the first dose due to the production of anti-KW-0761 (mogamulizumab) antibodies.

Following multiple IV administrations once a week for 13 weeks at doses of 2.5, 10 or 40 mg/kg, AUC from time 0 to 168 hours (AUC0-168) values of KW-0761 (mogamulizumab) (early and late in the study) reflected the differences in dose levels. There were no sex differences in the toxicokinetic (TK) data. Anti-KW-0761 (mogamulizumab) antibodies were not detected in any monkeys at any dose level.

In a 26-week multiple-dose study with once weekly doses of 2.5, 10, or 40 mg/kg, the maximum observed concentration (Cmax), AUC from time 0 to 7 days (AUC0-7days), and AUC from time 0 to infinity (AUCinf) of KW-0761 (mogamulizumab) increased as the dose level increased. The Cmax and AUC0-7days after repeated dosing increased when compared with those after the first dosing, yielding AUC0-7days accumulation ratios of 2.6 to 8.2 across all dose groups. In one animal at 2.5 mg/kg, KW-0761 (mogamulizumab) was not detected in plasma on and after Day 29 due to the production of anti-KW0761 (mogamulizumab) antibodies.

Distribution
After a single IV administration of [125I] KW-0761 (mogamulizumab) at a dose of 1.0 mg/kg to male cynomolgus monkeys, the extent of tissue distribution of the radioactivity was relatively low with the maximum tissue to plasma radioactivity ratio of 0.26. The elimination of radioactivity from all the tissues nearly paralleled that from plasma (implying no accumulation in tissues).

Metabolism and Excretion
Metabolism and excretion studies were not conducted. The expected metabolism of KW-0761 (mogamulizumab) is degradation to small peptides and amino acids.

Pharmacokinetics Interaction
No *in-vitro* or *in-vivo* pharmacokinetic interaction studies have been conducted to date. Based on the expected mechanism of metabolism (proteolysis), no drug-drug interactions are expected.

Nonclinical toxicology
Based on comparable binding affinity for cynomolgus monkey and human lymphocytes and pharmacological activity (reduction in CCR4 positive cells in peripheral blood) in cynomolgus monkeys, the cynomolgus monkey was selected for nonclinical safety assessments of KW-0761 (mogamulizumab).

Results from both single- and repeat-dose iv (up to 26 weeks) or subcutaneous (sc) (single-dose) nonclinical toxicology studies of KW-0761 (mogamulizumab) in cynomolgus monkeys have demonstrated an acceptable safety profile, supporting its continued clinical use up to the highest planned iv clinical dose of 1 mg/kg (dosing regimen).

2.2.8 Summary of clinical pharmacodynamics

Weekly doses of KW-0761 (mogamulizumab) at 1.0 mg/kg iv given for eight weeks resulted in marked reductions in CD4+ CD25+ CCR4+ cells, as the indicator of peripheral blood ATL cells, decreased immediately after the first dosing of KW-0761 (mogamulizumab), and remained almost completely suppressed over a long period of time also after the second dose. In addition, the number of CD4-positive CD25-+ Foxp3+ cells, as the indicator of peripheral blood regulatory T cells, decreased immediately after the first dose of KW-0761 (mogamulizumab), and also remained almost completely suppressed over a long period of time after the second dose.

Immunogenicity: T-cell Lymphomas
Plasma samples from two clinical studies, KW-0761-001 and KW-0761-002, were analyzed for the presence of anti-drug antibodies to KW-0761 (mogamulizumab) in a screening assay, if positive, continued with a confirmatory assay, and if positive, continued with a neutralizing assay (Study Report 10/065-021). A total of 263 samples were analyzed (252 for Study KW-0761-001 and 11 for Study KW-0761-002). A total of 7 subjects from Study KW-0761-001 showed positive screening assay results. No subject showed positive screening assay results from Study KW-0761-002. Four out of 7 subjects who tested positive in the screening assay showed positive results for the confirmatory assay in the post-treatment samples collected from Cycle 1 to 11 and at the final visits. One subject showed positive result for confirmatory assay in the pre-treatment sample only.

Previously, interference of KW-0761 (mogamulizumab) with the neutralizing assay at concentrations of 1 μg/mL and higher had been noted (Study Report 08/065-011). In Study KW-0761-001, plasma KW-0761 (mogamulizumab) concentration data were not considered to be reliable because the analytical method utilized to measure the plasma KW-0761 (mogamulizumab) concentrations did not yield acceptable results for incurred sample reanalysis. Therefore, despite negative final results, no conclusion can be drawn from the neutralizing assay data regarding the potential presence of neutralizing antibodies in the samples tested positive in the confirmatory assay.

2.2.9 Summary of clinical pharmacokinetics

The mean plasma concentration-time profiles and summary of pharmacokinetic parameters of mogamulizumab after eight repeated doses of 1.0 mg/kg of iv KW-0761 (mogamulizumab) at 1-week intervals in subjects with CCR4+ ATL based on a Phase 2 Repeated Dose Study in Subjects with CCR4+ ATL.

The mean Cmax and Ctrough increased as the number of doses increased over time; steady state was not reached after eight weekly doses. The mean cumulative ratio after the 8th administration was 2.25 for Cmax, 3.56 for Ctrough, and 2.87 for AUC0-7 days. The mean t1/2 after the 8th dose was 422 ± 147 hours (17.6 ± 6.1 days). The estimated Cmax and Ctrough, based on a two-compartment open model analysis of the mean plasma concentration data, were 40993.2 ng/mL and 29 546.4 ng/mL after the 8th administration, respectively. These model-predicted values were similar to the observed mean Cmax and Ctrough values, indicating that the pharmacokinetics of mogamulizumab was stable after repeated doses.

2.2.10 Rationale for KW-0761 (mogamulizumab) dose selection and schema

The dose of KW-0761 (mogamulizumab) planned to be studied in this trial is induction dosing of 1.0 mg/kg administered IV weekly for three weekly doses followed by maintenance dosing of 1.5mg/kg every 21 days until disease progression. Dosage of up to 1.0 mg/kg was approved in Japan for T-cell lymphomas. There is a high likelihood that induction dose of 1mg/kg will be safe and well tolerated as demonstrated in clinical trial with monotherapy KW-0761 (mogamulizumab). We are, however, including a de-escalation dose level of 0.5 mg/kg, 50% of starting dose. The maintenance dosing of every 21 days will allow for ease of administration with MK-3475 (pembrolizumab). To maintain dose intensity with every 21 days schedule (versus every 14 days schedule), the maintenance dosing will be increased to 1.5mg/kg. KW-0761 (mogamulizumab) has been given at doses of 3mg/kg in combination with durvalumab with no unexpected adverse events. Since the terminal half-life after 8-week therapy was found to be around 18 days, dosing every 21 days should still allow for substantial drug serum concentration at 21 days. Additional information on the rationale for dosage selecting is summarized below.

Pharmacokinetics of KW-0761 (mogamulizumab) following bi-weekly dosing of KW-0761 (mogamulizumab) in combination with mLSG15 was characterized in subjects with CCR4+ ATL (Study 0761-003). All of the 29 subjects who received KW-0761 (mogamulizumab) were included in the pharmacokinetic analysis set. The mean C_{max} and C_{trough} concentrations after repeated iv administrations every two weeks in subjects with CCR4+ ATL. After the 8th dose, the mean C_{max} and C_{trough} of KW-0761 (mogamulizumab) were 22814.3 ± 4634.1 ng/mL and 9420.9 ± 3845.6ng/mL, respectively. The R_{obs} of the 8th dose to the first dose for Cmax and Ctrough were 1.49 and 2.92, respectively.

Multiple phase I and II studies (KW-0761-001; KW-0761-002; 0761-007) with monotherapy KW-0761 (mogamulizumab), in the US and Europe, included patients with relapsed PTCL and CTCL. Phase 1 doses were 0.1, 0.3 and 1.0 mg/kg iv. Phase 2 dose was 1.0 mg/kg iv. The regimen was weekly for four weeks, then every other week until progression or DLT.

2.2.11 Summary of Safety

The most frequent treatment-emergent adverse events reported in phase I/II study in T-cell lymphomas were: nausea (31.0%), chills (23.8%), headache (21.4%), and infusion-related reaction (21.4%); the majority of events were grade 1/2. There were no significant hematologic effects (Duvic et al., 2015).

As of 30 Sep 2016, an estimated 3244 patients have received at least one dose of KW-0761 (mogamulizumab). The most frequently reported SAEs (occurring in three or more patients) considered to be at least possibly related to KW-0761 (mogamulizumab). Rash (1.26%), infusion reactions (1.05%), CMV infections (0.71%), pneumonia (0.71%), erythema (0.59%), febrile neutropenia (0.52%), leukopenia (0.46%), sepsis (0.40%), and SJS (0.46% overall and approximately 1% in Japanese patients) have been reported most frequently (Investigator's brochure 2016).

The potential complications observed in patients underwent hematopoietic stem cell transplantation after exposure to KW-0761 (mogamulizumab) supports the relevance of CCR4-expressing Tregs after allo-HSCT in humans. In patients treated with KW-0761 (mogamulizumab) who subsequently received HSCT, the incidence of GVHD is estimated to be 30% to 50% based on the total number of transplant recipients reported in the DURS and recent reports in the literature (Sugio et al., 2016; Inoue et al., 2016; Fuji et al., 2016). These reports indicate that KW-0761 (mogamulizumab) therapy prior to HSCT may be associated with more severe GVHD and poor outcomes post-transplant.
The importance of these findings is related to the possibility that HSCT may offer a curative treatment option for patients with aggressive ATL (Chihara et al., 2013; Fuji et al., 2016).

Care should be taken with the use of KW-0761 (mogamulizumab) in patients who have received HSCT or may go on to HSCT as CCR4 is expressed not only on tumor cells but also on normal regulatory T cells and Th2 cells, cells that may influence immune reconstitution and occurrence of GVHD post-transplant. Patients should be monitored for complications of allo-HSCT after KW-0761 (mogamulizumab). Exposure to KW-0761 (mogamulizumab) should be considered when evaluating a patient for transplant and appropriate methods to prevent or mitigate GVHD should be strongly considered (Investigator's Brochure 2016).

2.3 Rationale

An emerging therapeutic strategy for relapsed, refractory diffuse large B-cell lymphoma has been to augment the host immune response. The extent of the host immune response, as demonstrated by the presence tumor-infiltrating effector CD8+ T cells and the ratio of effector to regulatory T cells, correlates with therapeutic outcomes in various lymphomas. The use of allogeneic transplant and donor lymphocyte infusions to promote durable remissions further emphasizes the potential for tumor immunotherapy in lymphoma. DLBCL has been shown to suppress the host immune response via a variety of mechanisms. These include genetic deletion of genes required for anti-tumor T-cell responses such as beta-2 microglobulin and CD58 (Challa-Malladi et al., 2011; de Miranda et al., 2014), which prevent recognition by effector CD8 and NK cells, respectively, as well as pathologic upregulation of ligands for the inhibitory receptor Programmed

Cell Death-1 (PD-1) (Chen et al., 2013; Georgiou et al., 2016; Kataoka et al., 2016; Laurent et al., 2015). PD-1 is normally engaged on T-cells following activation in order to appropriately limit the extent of T-cell responses to foreign antigens, but in lymphomas, abnormal expression of PD-1 ligands results in inappropriate suppression of anti-tumor responses. Targeting this negative regulatory interaction has resulted in dramatic clinical responses in solid tumors and has more recently shown promising activity in multiple lymphomas, including Hodgkin lymphoma (HL) and follicular lymphoma (FL), with responses rates of 50-80% and 40%, respectively in patients with multiply relapsed disease (Armand et al., 2016; Lesokhin et al., 2016; Younes et al., 2016). MK-3475 (pembrolizumab) is thought "unlicense" tumor-infiltrating T-cells, permitting anti-tumor responses to low-affinity neoantigens that would otherwise be ineffective at inducing productive T-cell activation. Treatment of DLBCL with nivolumab, a humanized IgG4 monoclonal antibody that binds PD-1, resulted in responses in 36% of patients with DLBCL in a phase I study, but responses were transient with a median duration of response of only 7 weeks (Lesokhin et al., 2016). This suggests that alternative immunosuppressive mechanisms exist within the DLBCL tumor microenvironment that continues to restrain effective anti-tumor responses, even in the presence of PD-1 blockade.

One potential contributor to persistent immunosuppression in the setting of checkpoint blockade is the presence of intratumoral regulatory T-cells (Tregs). Tregs are a subset of CD4+ T cells that are required to restrain excessive immune responses to foreign pathogens and restrain tissue damage and autoimmunity. However, these immunoregulatory properties may pathologically promote malignancy by inappropriately restraining effector responses. This is best exemplified by the observed regression of established tumors in experimental models of Treg depletion (Klages et al., 2010; Li et al., 2010; Teng et al., 2010). While the immunosuppressive targets of Tregs has most classically been tumor-infiltrating effector T-cells, recent work from Alexander Rudensky's group has demonstrated that Tregs play a critical role in suppressing NK cell-mediated killing of MHC class-I deficient targets (Gasteiger et al., 2013).

There is strong evidence to suggest that lymphomas recruit Tregs to suppress anti-tumor immunity. B-cell lymphomas have been shown to produce chemokines that serve as chemoattractants to induce Treg recruitment into the tumor microenvironment. In particular, production of CCL22 (MDC) and CCL17 (TARC) has been resported in multiple lymphomas (Ghia et al., 2001; Takegawa et al., 2008; Niens et al., 2008). These chemokines recruit Tregs through the chemokine receptor CCR4, a lymphocyte receptor expressed on Tregs (Tobinai et al., 2012). Production of CCL17 and CCL22 in lymphomas has been shown to recruit CCR4+ Tregs into the tumor microenvironment (Yang et al., 2006). The recruitment of Tregs to the tumor microenvironment may underlie ineffective NK cell cytotoxicity seen in DLBCL (Cox et al., 2015). We have preliminary observed that patients progressing on anti-PD-1 therapy have a high proportion of Tregs within the tumor microenvironment, which may promote ongoing immune evasion in the presence of checkpoint blockade.

This suggests that depletion of Tregs may be an effective therapeutic strategy to promote anti-tumor immune responses. Indeed, work by Jedd Wolchok's group at MSKCC has demonstrated that many immunomodulatory therapeutic strategies (such as GITR agonists, indoleamine 2,3 dioxygenase inhibitors, or anti-CTLA-4 antibodies) may operate through intratumoral Treg depletion (Schaer et al., 2013; Holmgaard et al., 2013; Simpson et al., 2013). CCR4 is a highly

attractive strategy for therapeutic targeting of Tregs as it is preferentially expressed on activated regulatory T-cells, which exert a more potent immunosuppressive effect (Hirahira et al., 2006). Indeed, CCR4 antagonism in mouse models induced expansion of antigen-specific CD8 T cells and promoted anti-tumor immunity (Pere et al., 2011). In a phase I/II study of subjects with relapsed adult T-cell leukemia/lymphoma (ATLL), a single treatment course of KW-0761 (mogamulizumab) (8 weekly doses of 1 mg/kg) induced a marked depletion of FoxP3+ Tregs from the peripheral blood that persisted for 4 months after the final dose (Ishida et al., 2012; Sugiyama et al., 2013). In CTCL patients, treatment with KW-0761 (mogamulizumab) effectively depleted CC4+ Tregs leading to an increase in CD8 and NK cell cytotoxicity (Ni et al., 2015); similar results were seen in a phase Ia clinical trial of solid tumor patients in which KW-0761 (mogamulizumab) depleted circulating Tregs and induced peripheral blood responses to cancer/testis antigens (Kurose et al., 2015).

We propose that targeting regulatory T cells with the monoclonal antibody KW-0761 (mogamulizumab), a humanized monoclonal antibody targeting the chemokine receptor CCR4 that is highly expressed on Tregs, represents a mechanistically rational strategy to overcome resistance to checkpoint blockade and promote durable responses in relapsed and refractory diffuse large B-cell lymphoma. KW-0761 (mogamulizumab) has been safely administered to patients with T cell lymphomas (Duvic et al., 2015; Ogura et al., 2014; Zinzani et al., 2016; Yamamoto et al., 2010). We propose that the combination of KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) will overcome immune evasion in DLBCL by promoting CD8 T-cell dependent effector responses in MHC-I expressing lymphomas while promoting NK cell-dependent cytotoxicity in MHC-I deficient lymphomas.

2.4 Correlative Studies Background

2.4.1 Targeted genomic sequencing and fluorescence in-situ hybridization of formalin-fixed, paraffin-embedded tumor samples

2.4.1.1 Background

The MSK-IMPACT platform is a CLIA-certified assay which routines assays for somatic mutations in clinical FFPE samples, achieving >500X coverage in almost all samples. The Clinical Cytogenetics Laboratory has developed multiple FISH assays, including PD-L1, for clinical use.

2.4.1.2 Hypotheses

1) DLBCL tumors with somatic mutations in B2M and CD58 will be differentially associated with tumor-infiltrating CD8 and NK cells in response to KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab), with NK cell predominant responses in B2M-mutant DLBCL and CD8 T-cell predominant responses in CD58-mutant DLBCL
2) Genetic amplification of PD-L1 will predict for response to therapy

2.4.1.3 Aims

1) Determine the prevalence of somatic mutations in B2M and CD58 in patients treated

with KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) vs. MK-3475 (pembrolizumab) alone and correlate with progression-free survival
2) Determine the prevalence of PD-L1 amplifications by FISH and correlate with progression-free survival

2.4.1.4 Methods

DNA extracted from formalin-fixed, paraffin-embedded tissues will be evaluated for somatic mutations in established cancer-related genes using the MSK-IMPACT hybrid capture platform (Hyman et al., 2015, Cheng et al., 2015) which includes over 400 genes commonly mutated in hematologic malignancies including those listed above. Amplification of PD-L1 will be evaluated by fluorescence in-situ hybridization (Roemer et al., 2016) in the Clinical Cytogenetics Laboratory.

2.4.2 Immunohistochemical analysis of the tumor and tumor microenvironment

2.4.2.1 Background

The MSK Pathology department has extensive expertise in performing Immunohistochemical assessment of CD3, CD4, CD8, MHC-I, MHC-II, B2M, PD-L1, CCR4, and FoxP3. Association of expression levels of these proteins with outcomes in Hodgkin lymphoma was presented at the 2016 American Society of Hematology meeting.

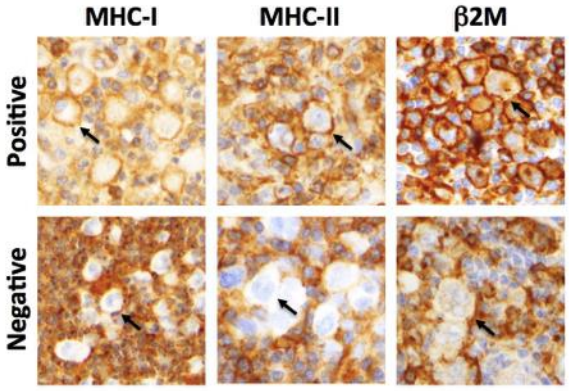

Figure 1. Example of positive and negative staining for MHC-I, MHC-II, and B2M in Hodgkin lymphoma samples.

2.4.2.2 Hypotheses

1) DLBCL tumors with loss of surface MHC-I expression will be associated with higher NK cell infiltration while tumors with surface loss of CD58 will be associated with higher CD8 T cell infiltration in response to therapy

Depletion of tumor-infiltrating regulatory T-cells (marked by FoxP3 expression) will predict for response to therapy.

2.4.2.3 Aims

1) Determine expression levels of MHC-I, CD58, PD-L1, and FoxP3 at baseline and in response to therapy using Immunohistochemical analysis of FFPE samples obtained prior to and following 1 cycle of therapy, and correlate these results with progression-free survival.

2.4.2.4 Methods

Immunostaining of FFPE sections from pre-treatment biopsies will be performed as previously described; all targets have been validated and successfully used in patients with lymphoma (Vardhana et al., Blood 2016). Expression of MHC-I, MHC-II, and CD58 will be scored in a binary fashion (positive vs. negative) while CD3, CD4, CD8, PD-L1 and

FoxP3 expression will be scored based on percent of total cells that are positive across 15 high-powered fields. Results will be independently corroborated by 2 pathologists.

2.4.3 Immunophenotyping and functional characterization of circulating immune cells

2.4.3.1 Background

The Immune Monitoring Facility is a CLIA-certified laboratory with extensive experience in performing the assays mentioned below, as shown in Figure 2, demonstrating a significant reduction in circulating regulatory T cells (A) and increase in CD8 T cells (B) in the peripheral blood following treatment with KW-0761 (mogamulizumab) in a phase I trial.

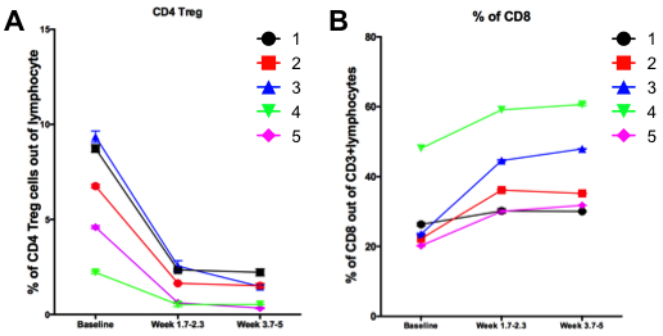

Figure 2. Depletion of regulatory T cells (A) and enhancement of CD8 T cells (B) in patients treated with mogamulizumab in a phase I trial. Each number represents a separate patient.

2.4.3.2 Hypotheses

1) KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab) will decrease regulatory T cells in the peripheral blood
2) KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab) will result in an increase in the activation status and effector function of circulating T cells within the peripheral blood.

2.4.3.3 Aims

1) Determine the prevalence of circulating regulatory T-cells in the peripheral blood following treatment with KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab)
2) Determine the prevalence, activation status, and effector function of circulating T-cells in the peripheral blood following treatment with KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab)

2.4.3.4 Methods

Flow cytometry will be performed within the Immune Monitoring Facility at MSKCC.
Flow cytometric assessment of the lymphocyte subsets $CD4^+$, $CD8^+$, $CD16^+$, $CD19^+$ and CD56+ will be examined as percent and absolute number. $FOXP3^+$ and $FOXP3^-$ lymphocytes with the following markers will also include but not limited to: $CD4^+$, CD25, CCR4, CD45RA, CD45RO, LAG3, GARP, PD1, and CTLA4 (Figure 2). Activation markers such as CD44 and CD69, will also be examined.

2.4.4 Evaluation of circulating serum cytokines at baseline and in response to therapy

2.4.4.1 Background

The Immune Monitoring Facility is a CLIA-certified laboratory with extensive experience

in performing the assays mentioned above, and has published identical assays performed as part of early phase trials of ipilimumab and nivolumab in solid organ malignancies.

2.4.4.2 Hypotheses

An increase in the production of pro-inflammatory cytokines (IFN-g, IL-2, TNF-a) and a decrease in anti-inflammatory cytokines (IL-10) will be seen in response to therapy.

2.4.4.3 Aims

Determine levels of IL-2, IL-4, IL-6, IL-10, TNF-a, IFN-g, and IL-17a in patient serum following treatment with KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab).

2.4.4.4 Methods

Cytokine measurements will be performed on serum by the Immune Monitoring Facility using a Human Th1/Th2/Th17 cytometric bead array (BD Biosciences). Cytokines measured will include IL-2, IL-4, IL-6, IL-10, TNF-a, IFN-g, and IL-17a.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed diffuse large B-cell lymphoma. All subtypes of diffuse large B-cell lymphoma are eligible, including high-grade B-cell lymphoma (Swerdlow et al., 2016) and DLBCL that has transformed from a prior indolent B-cell Non-Hodgkin lymphoma.

3.1.2 Patients must have measurable disease per 2014 Lugano Classification Criteria (Cheson et al., 2014) which is defined as at least one nodal lesion measuring >1.5cm in greatest diameter or at least one extranodal lesion measuring >1.0cm in greatest diameter.

3.1.3 For phase 2: patients have received at least 2 prior lines of therapy and must have previously received, refused, or been deemed ineligible for autologous stem cell transplantation.

3.1.4 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of MK-3475 (Pembrolizumab) in combination with KW-0761 (Mogamulizumab) in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status ≤ 1 (Karnofsky ≥ 80%, see Appendix A).

3.1.6 Patients must have normal organ and marrow function as defined below:

Absolute neutrophil count	≥1,500/mcL (if neutropenia is related to bone marrow involvement with lymphoma, the absolute neutrophil count must be ≥1,000/mcL)
Platelets	≥75,000/mcL (if thrombocytopenia is related to bone marrow involvement with lymphoma, the platelet count must be ≥50,000/mcL)
Hemoglobin	≥9 g/dL (if anemia is related to bone marrow involvement with lymphoma, the hemoglobin must be ≥8 g/dL)
Total bilirubin	≤1.5x the institutional ULN or < 3x the ULN for indirect bilirubin in patients with Gilbert's disease
AST and ALT	≤2.5x institutional upper limit of normal
Creatinine OR measured or calculated creatinine clearance	≤1.5x institutional upper limit of normal **OR** if creatinine >1.5x ULN then creatinine clearance ≥40 mL/min/1.73 m^2 as calculated by Cockcroft and Gault equation

3.1.7 Life expectancy of greater than 3 months

3.1.8 The effects of MK-3475 (Pembrolizumab) in combination with KW-0761 (Mogamulizumab) on the developing human fetus are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and 6 months after completion of MK-3475 (Pembrolizumab) in combination with KW-0761 (Mogamulizumab) administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion of MK-3475 (Pembrolizumab) in combination with KW-0761 (Mogamulizumab) administration.

Submit adequate archival tissue specimen (25+ unstained slides or 2 tissue blocks) from a biopsy performed after progression of disease on most recent therapy OR subject is willing to undergo a new core or excisional biopsy to obtain evaluable tumor tissue sample for immunohistochemical assessment and sequencing for B2M loss. Repeat samples may be required if adequate tissue is not provided, however, patients may still be considered for enrollment on a case by case basis following consultation with the PI. See Section 2.4 in protocol for an explanation.

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

3.1.10 Subjects with prior history of chemotherapy-induced or radiation-induced pulmonary toxicity require confirmation of diffuse capacity of the lung for carbon monoxide (DLCO) over 60% (adjusted for hemoglobin) by a pulmonary function test prior to study enrollment.

3.2 Exclusion Criteria

3.2.1 Patients who have had previous systemic anti-cancer therapy within 2 weeks or 5 half-lives (the shorter of the two) of registration or those who have not recovered from adverse events due to agents administered previously.

Note: Patients are considered enrolled on the study after protocol registration and not after signing consent.

3.2.2 Patients who are receiving any other concurrent investigational agents.

3.2.3 Patient is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids (e.g. prednisone <=20mg/d) may be approved after consultation with the study PI. Topical or inhaled corticosteroids are allowed.

3.2.4 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 that has undergone potentially curative therapy, or *in situ* cervical cancer.

3.2.5 Patients with active cerebral or meningeal involvement by lymphoma should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound evaluation of neurologic and other adverse events.

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-3475 (Pembrolizumab) or KW-0761 (Mogamulizumab).

3.2.7 Subject with active autoimmune disease. Subjects with vitiligo, eczema, alopecia, type I diabetes mellitus, psoriasis not requiring systemic treatment, or endocrine deficiencies (such as hypothyroidism) managed with replacement hormones, including physiologic corticosteroid replacement therapy are eligible.

3.2.8 Has a history or currently active (non-infectious) pneumonitis that required steroids unless prior history of chemotherapy or radiotherapy induced pneumonitis meeting the eligibility criteria in 3.1.11

3.2.9 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

3.2.10 Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

3.2.11 Prior allogeneic SCT

3.2.12 Patients who are planning to receive allogeneic SCT in the near future as preliminary reports suggest added toxicity in patients undergoing allogeneic stem cell transplantation after having received mogamulizumab.

3.2.13 Autologous SCT ≤ 90 days prior to first dose of study drug

3.2.14 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, interstitial lung disease or active, non-infectious pneumonitis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.15 Pregnant women are excluded from this study because MK-3475 (pembrolizumab) is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MK-3475 (pembrolizumab), breastfeeding should be discontinued if the mother is treated with MK-3475 (pembrolizumab). These potential risks may also apply to KW-0761 (mogamulizumab).

MK-3475 (pembrolizumab) and KW-0761 (mogamulizumab) may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 (pembrolizumab) or KW-0761 (mogamulizumab) has transient adverse effects on the composition of sperm. Patients are excluded from this study if pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of trial treatment.

See Section 5.7 for information on contraception and pregnancy.

3.2.16 Patients with HIV are excluded if they have a detectable viral load, are not on a stable antiretroviral regimen, have a decreased CD4+ T-cell count (<500), or require prophylactic antibiotics for the prevention of opportunistic infections.

3.2.17 Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority

3.2.18 Has a known history of active tuberculosis (TB).

3.2.19 Patients with significant cardiac disease (e.g., NYHA class III-IV congestive heart failure, unstable angina, recent myocardial infarction within the last 6 months, etc.).

3.3 Inclusion of Women and Minorities

Both and women of all races and ethnic groups are eligible for this trial.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	2	2	2	**8**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Native Hawaiian or Other Pacific Islander	1	1	1	1	**4**
Black or African American	6	6	2	2	**16**
White	15	15	4	4	**38**
More Than One Race	3	3	2	2	**10**
Total	**27**	**27**	**11**	**11**	**76**

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4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval Log (DTL).

Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

- Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to:
- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the *[NCI protocol #]* protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MD017 and protocol #10106

- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10106 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- A Site initiation visit (SIV) is required for each participating site prior to activation. The local site PI must participate on the call as well as their research nurse, study coordinator, and pharmacist. To schedule a SIV, please email the Protocol Liaison and crocc@jhmi.edu and reference the protocol in the subject line of the email.

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does

not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 Patient Enrollment Instructions

Slot reservation will not be used when enrolling subjects. Slots are available on a first come, first serve basis.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website:

http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

As of 08/10/2019, we are using dose level (-1) due to limited feasibility of administering dose level 1.

Dose Escalation Schedule		
Dose Level	**Dose**	
	MK-3475 [Pembrolizumab] (mg)	**KW-0761 [Mogamulizumab] (mg/kg)**
Level -1	200mg IV day 1 every 21 days	Induction: 0.5 mg/kg IV weekly for 3 weeks Maintenance: 1mg/kg IV day 1 every 21 days
~~Level 1~~	~~200mg day 1 every 21 days~~	~~Induction: 1 mg/kg IV weekly for 3 weeks~~ ~~Maintenance: 1.5mg/kg IV day 1 every 21 days~~

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
MK-3475 (Pembrolizumab)	N/A	200 mg	IV Piggyback (IVPB) over 30 minutes.	Every 3 weeks (Day 1 of each cycle)	21 days (3 weeks)
KW-0761 (Mogamulizumab)	Premedication with acetaminophen orally, diphenhydramine 50mg IV (or equivalent), hydrocortisone 50mg IV before the first and second KW-0761 (mogamulizumab) infusion. If a subject experiences an infustion-related reaction at any time during the study, pre-	According to assigned dose level*	IVPB over 60 minutes. After the first dose, a 4-hour observation period is required. A minimum one-hour post-dose observation period is required after	Weekly for 3 weeks (C1D1, C1D8, C1D15) then once every 3 weeks (C2D1, C3D1, etc.)	

	medication is recommended prior to subsequent infusions.		each infusion.		

*The dose of KW-0761 (mogamulizumab) will be as is appropriate for the assigned dose level in the phase I part of the study. In the phase II part of the study, KW-0761 (mogamulizumab) dose will be administered at the MTD / RP2D.

In the phase I, the starting dose level is Level 1 (see Table above entitled Dose Escalation Schedule). Dose Level 1 consists of MK-4375 (pembrolizumab) given 200mg IV every 3 weeks and KW-0761 (mogamulizumab) 1mg/kg once weekly for 3 weeks (C1D1, C1D8, C1D15) and thereafter maintenance KW-0761 (mogamulizumab) 1.5mg/kg on day 1 of every 21-day cycle (C2D1, C3D1, etc). As of 08/10/2019, we are using dose level (-1) due to limited feasibility of administering dose level 1.

For the randomized phase II, patients will be assigned to one of two treatment groups, Group 1 (MK-3475 [pembrolizumab] and KW-0761 [mogamulizumab]) and Group 2 (MK-3475 [pembrolizumab] alone). Patients will receive either MK-3475 (pembrolizumab) 200mg IV on day 1 of every 21-day cycle and KW-0761 (mogamulizumab) at the induction RP2D once weekly for 3 weeks (C1D1, C1D8, C1D15) and thereafter at the maintenance RP2D on day 1 of every 21-day cycle (C2D1, C3D1, etc) (Group 1) or MK-3475 (pembrolizumab) alone (Group 2).

5.1.1 MK-3475 (pembrolizumab)

Trial treatment of MK-3475 (pembrolizumab) will be administered on Day 1 of each 3-week treatment cycle after all procedures/assessments have been completed. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (up to 5 days after randomization is permitted).

MK-3475 (pembrolizumab) will be administered as a dose of 200 mg using a 30-minute IV infusion. Infusion timing should be as close to 30 minutes as possible; however, a window of minus 5 minutes and plus 10 minutes is permitted (i.e., infusion time is 25 – 40 minutes). Refer to section 6 for compatible infusion set materials including in-line filter.

Administration: Mild infusion reactions can generally be treated with interruption of the infusion and medical intervention, including IV fluids, antihistamines, nonsteroidal anti-inflammatory drugs, acetaminophen, and narcotics as needed. More severe or life-threatening reactions may require vasopressors, corticosteroids, and epinephrine. In the case of severe or life-threatening reactions, subsequent doses of pembrolizumab should not be administered.

5.1.2 KW-0761 (mogamulizumab)

Trial treatment of KW-0761 (mogamulizumab) will be administered on Day 1, 8, and 15 of cycle 1 and on Day 1 of all subsequent 21 day treatment cycles after all procedures/assessments have been completed. Trial treatment may be administered up to 2 days before or after the scheduled date during cycle 1 and 3 days before or after the scheduled treatment date of each consecutive cycle due to administrative reasons (in order to ensure at least 5 days between doses).

KW-0761 (mogamulizumab) will be administered as the dose that is appropriate per dose level during dose escalation or at the RP2D using a 60-minute IV infusion. Infusion timing should be as close to 60 minutes as possible. KW-0761 (mogamulizumab) will be administered after MK-3475 (pembrolizumab). After first dose of KW-0761 (mogamulizumab) (C1D1), patients will be monitored for a minimum of four hours to monitor for potential infusion reaction. Thereafter, patients will be monitored for one-hour after KW-0761 (mogamulizumab) administration.

It is recommended that subjects be pre-medicated with acetaminophen 650 mg orally, diphenhydramine 50 mg IV (or equivalent), and hydrocortisone 50mg IV before the *first and second* KW-0761 (mogamulizumab) infusion. If a subject experiences an infusion-related reaction at any time during the study, pre-medication is recommended prior to subsequent infusions.

See section 6 for management of infusion reactions to KW-0761 (mogamulizumab).

5.2 Definition of Dose-Limiting Toxicity

The DLT window of observation will be the first 2 cycles (6 weeks).
The occurrence of any of the following toxicities will be considered a DLT, except those AEs that are clearly and incontrovertibly due to extraneous causes:

1. Grade 4 hematologic toxicity lasting ≥7 days. Lymphopenia, a pharmacologic effect of the antibody treatment, will not be considered a DLT
2. Any Grade 3 or 4 non-hematologic toxicity (not laboratory) of any duration. Exceptions include:
    - Grade 3 fatigue, asthenia, fever, anorexia, or constipation
    - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization

3. Any Grade 3 or Grade 4 nonhematologic laboratory value if:

    - Medical intervention is required to treat the patient, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >72 hours.
    - **The only exception for the above criteria is an isolated grade 3 increase in amylase or lipase not associated with clinical signs or symptoms of pancreatitis- this will not be considered a DLT.**

4. Febrile neutropenia Grade 3 or Grade 4.

5. Grade 3 or 4 thrombocytopenia if associated with clinically significant bleeding.

6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.

7. Grade 5 toxicity.

8. Patients meeting criteria for Hy's Law (ALT or AST >= 3x ULN and ALP <2x ULN and BIL >= 2x ULN) among patients with normal ALT, AST, ALP, and BIL measurements during the baseline period (30 days prior to initiation of study drug). Normal is defined as an ALT, AST, ALP, and BIL <1 times the upper limit of normal at baseline. ALT is alanine aminotransferase, AST is aspartate transaminase, ALP is alkaline phosphatase, and BIL is bilirubin.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed according to the following scheme. Dose-limiting toxicity (DLT) is defined above. In this study, patients will be initially enrolled at dose level 1 and only if there are excessive DLTs will there be dose de-escalation.

Number of Patients with DLT at a Dose Level 1	**Escalation Decision Rule**
0 out of 3	Enter an additional 3 patients at dose level 1. If ≤1 out of 6 experience DLT, dose level 1 will be declared the RP2D.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, dose level 1 will be declared the RP2D. • If 1 or more of this group suffer DLT, then dose level 1 will be declared the maximally administered dose. Three patients will be entered at dose level -1.
≥2	Dose level 1 will be declared the maximally administered dose (highest dose administered). Three patients will be entered at dose level -1.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the RP2D

Number of Patients with DLT at a Dose Level -1	**Escalation Decision Rule**
0 out of 3	Enter an additional 3 patients at dose level -1. If ≤1 out of 6 experience DLT, dose level -1 will be declared the RP2D.

1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, dose level -1 will be declared the RP2D. • If 1 or more of this group suffer DLT, then dose level -1 will be declared the maximally administered dose. The study will require amendment to test a lower dose level.
≥2	Dose level -1 will be declared the maximally administered dose (highest dose administered). The study will require amendment to test a lower dose level.

5.3 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of MK-3475 (Pembrolizumab) and KW-0761 (Mogamulizumab) with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of.
Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with CTEP. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician; however, the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, CTEP, and the patient.

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

All concomitant medications received within 30 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.
Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAEs).

Prohibited Concomitant Medications
Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.

- Immunotherapy or immunosuppressants not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than MK-3475 (pembrolizumab) or KW-0761 (mogamulizumab).
- Radiation therapy - The use of palliative radiotherapy should be minimized given the potential of such treatment to confuse assessments of study drug safety and therapeutic effect. However, administration of limited-fraction radiotherapy is permitted after Cycle 1 to control local tumor-related symptoms if irradiation is unlikely to induce major organ toxicity or affect target lesions being followed for tumor response and progression.
- Live vaccines while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the study PI and CTEP.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the investigator deems to be medically necessary.
The Exclusion Criteria describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4 Duration of Therapy

In the absence of treatment delays due to AE(s), treatment may continue for up to 2 years or until 1 of the following criteria applies:

- Disease progression
- Intercurrent 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
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.5 Criteria to Resume Treatment

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.6 Contraception and Pregnancy

5.6.1 Contraception

MK-3475 (pembrolizumab) may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 (pembrolizumab) has transient adverse effects on the composition of sperm.

KW-0761 (mogamulizumab) may have adverse effects on a fetus in utero. It has not been evaluated in pregnant or lactating women.

For this trial, male patients will be considered to be of nonreproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of nonreproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
   OR
2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
   OR
3. Has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 180 days after the last dose of study drug by complying with one of the following:

1. Practice abstinence[†] from heterosexual activity;

OR

2. Use (or have their partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

Single method (1 of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients 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, patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 180 days after the last dose of trial therapy.

If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

5.6.2 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with MK-3475 (pembrolizumab) or KW-0761 (mogamulizumab), the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported without delay and within 24 hours 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. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported and followed.

5.6.3 Use in Nursing Women

It is unknown whether MK-3475 (pembrolizumab) or KW-0761(mogamulizumab) 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, patients who are breast-feeding are not eligible for enrollment.

5.7 Treatment Beyond Progression

Immunotherapeutic agents such as MK-3475 (pembrolizumab) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

A new response category called "indeterminate response" (IR) was developed based upon experience with checkpoint blockade therapy in which response assessment may be confounded by the delayed effect of these drugs, allowing for early tumor growth, or therapeutic immune activation that can manifest as growth of existing lesions or development of new lesions, resulting in delayed response or pseudo-progression. Please see the section entitled "Measurement of Effect" for the definition of IR.

If radiologic imaging shows IR, tumor assessment may be repeated by the site ≥4 weeks later with the option of continuing treatment per below while awaiting clarification of response. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating IR, treatment may be continued as per treatment calendar. If repeat imaging confirms true PD, patients will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. The decision to continue study treatment after the 1st evidence of disease progression determined by radiologic imaging is at the Investigator's discretion based on the clinical status of the patient as described in the table below.

Patients may receive study treatment while waiting for clarification of response if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression)

requiring urgent alternative medical intervention

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of IR	Repeat imaging at ≥4 weeks to clarify response	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥4 weeks to clarify response per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

5.8 Discontinuation of Treatment Following Complete Response

Discontinuation of treatment may be considered for patients who have attained a confirmed complete response (CR) that have been treated for at least 24 weeks with MK-3475 (pembrolizumab) and had at least four cycles of treatment with MK-3475 (pembrolizumab) and KW-0761 (mogamulizumab) beyond the date when the initial CR was declared.

5.9 Treatment Up to 2 Years

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 2 years with MK-3475 (pembrolizumab) (maximum 35 cycles) with or without KW-0761 (mogamulizumab) (maximum 34 cycles) or until one of the following criteria applies: documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the patient, patient withdraws consent, pregnancy of the patient, noncompliance with trial treatment or procedure requirements, or administrative reasons.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose modifications and supportive care guidelines for drug-related adverse events with the combination of MK-3475 (Pembrolizumab) and KW-0761 (Mogamulizumab).

Adverse events (both non-serious and serious) associated with MK-3475 (pembrolizumab) and KW-0761 (mogamulizumab) exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Study regimen must be withheld for drug-related toxicities and severe or life-threatening AEs as the table in Section 6.1.2.

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

6.1.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are also outlined in the table in Section 6.1.2. Where appropriate, these guidelines include the use of oral or IV 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 progressive 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 MK-3475 (pembrolizumab) or KW-0761 (mogamulizumab).

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below).

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of the evaluation of the event.

6.1.2 Dosing Modification and Toxicity Management

Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) The event stabilizes and is controlled. 2) The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3) Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently	It is recommended that management of irAEs follows the guidelines presented in this table: • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections). • In the absence of a clear alternative etiology, all events should be considered potentially immune related. • Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. • For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. • If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). • More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. • Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Dose Modifications	Toxicity Management
discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	

AE=Adverse event; CTC=Common Toxicity Criteria; CTCAE=Common Terminology Criteria for Adverse Events; irAE=Immune-related adverse event; IV=intravenous; NCI=National Cancer Institute; PO=by mouth

6.2 Specific Immune-mediated Reactions

Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of

	Recurrent Grade 3 or Grade 4	Permanently discontinue	equivalent) followed by taper	bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4	Withhold [d]	• Initiate insulin replacement therapy	• Monitor participants for hyperglycemia or other

	hyperglycemia associated with evidence of β-cell failure		for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

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

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

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

6.3 Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	For Any Grade: Manage per institutional standard at the discretion of investigator. Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	For Grade 1: The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. For Grade 2: The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	For Grade 1 or 2: Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. Consider premedication per institutional standard prior to subsequent doses. Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** • Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE=Common Terminology Criteria for Adverse Events; IM=Intramuscular; IV=Intravenous; NCI=National Cancer Institute.

6.4 Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (e.g., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Medical Monitor." AE=Adverse event; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute.

6.5 Tumor lysis syndrome

In the event a patient develops tumor lysis syndrome, the patient will be managed per institutional guidelines.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agents

7.1.1.1 CAEPR for MK-3475 (pembrolizumab)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 27, 2019[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for KW-0761 (mogamulizumab)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for KW-0761 (mogamulizumab, NSC 791064)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4759 patients.* Below is the CAEPR for KW-0761 (mogamulizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, September 15, 2019[1]

Adverse Events with Possible Relationship to KW-0761 (mogamulizumab) (CTCAE 5.0 Term) [n= 4759]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CARDIAC DISORDERS			
		Chest pain - cardiac	
		Myocardial infarction	
		Myocarditis[2]	
		Restrictive cardiomyopathy	
GASTROINTESTINAL DISORDERS			
	Nausea		***Nausea (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Flu like symptoms[2]		
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		
		Anaphylaxis[3]	
		Immune system disorders - Other (graft versus host disease)[4]	
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		***Infusion related reaction[3] (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased[2,6]		

Adverse Events with Possible Relationship to KW-0761 (mogamulizumab) (CTCAE 5.0 Term) [n= 4759]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alkaline phosphatase increased[2,6]		
	Aspartate aminotransferase increased[2,6]		
	Blood bilirubin increased[2,6]		
	GGT increased[2,6]		
	Lymphocyte count decreased[2]		***Lymphocyte count decreased[2] (Gr 2)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr 2)***
	Platelet count decreased[2]		***Platelet count decreased[2] (Gr 2)***
	White blood cell decreased[2]		***White blood cell decreased[2] (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
NERVOUS SYSTEM DISORDERS			
	Peripheral motor neuropathy[2]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[2]	
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (drug eruption, toxic skin eruption)[2]	
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving KW-0761 (mogamulizumab). Adverse events potentially related to KW-0761 (mogamulizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KW-0761 (mogamulizumab), administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of KW-0761 (mogamulizumab), may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of KW-0761 (mogamulizumab).

[4]Acute graft-versus-host disease has been observed in patients treated with KW-0761 (mogamulizumab) who subsequently received hematopoeitic stem cell transplants.

[5]Infection may include any of the infection sites under the INFECTIONS AND INFESTATIONS SOC.

[6]Symptoms of hepatic dysfunction may include Alanine aminotransferase increased, Alkaline phosphatase increased, Aspartate aminotransferase increased, Blood bilirubin increased, and GGT increased under the INVESTIGATIONS SOC.

Adverse events reported on KW-0761 (mogamulizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that KW-0761 (mogamulizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrial fibrillation; Sinus tachycardia; Supraventricular tachycardia
EYE DISORDERS - Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal pain; Cheilitis; Colitis[2]; Constipation; Diarrhea; Gastritis; Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Generalized edema; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone); Hepatobiliary disorders - Other (hepatitis)
INVESTIGATIONS - Blood lactate dehydrogenase increased[2]; CPK increased; Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Acidosis; Anorexia; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (tendonitis); Myositis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Encephalopathy; Headache; Nervous system disorders - Other (altered state of consciousness); Nervous system disorders - Other (cerebellar syndrome); Paresthesia; Seizure
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Cough; Dyspnea; Hypoxia; Pleural effusion; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythroderma; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (lichenoid keratosis); Urticaria
VASCULAR DISORDERS - Hypertension[2]; Hypotension[2]

Note: KW-0761 (mogamulizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - 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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for

other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.
Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Pregnancy loss is defined in CTCAE as "Death in utero." Any pregnancy loss should be reported expeditiously, as **Grade 4 "Pregnancy loss"** under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days

Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

Not applicable.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

*The following paragraph **only** applies to trials using **Medidata Rave**; other trials may delete:*
Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP)

and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 MK-3475 (pembrolizumab) (NSC 776864)

Other Names: SCH 900475, pembrolizumab

Classification: Anti-PD-1 MAb

Molecular Weight: 148.9-149.5 KDa

CAS Number: 1374853-91-4

Mode of Action: The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells to suppress immune control. MK-3475 (pembrolizumab) blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands.

Description: MK-3475 (pembrolizumab) is a humanized MAb of the IgG4/kappa isotype.

How Supplied: MK-3475 (pembrolizumab) is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 100 mg vials containing a sterile, non-pyrogenic, clear to opalescent aqueous solution (25 mg/mL). Proteinaceous particles may be present. MK-3475 solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

Preparation: MK-3475 (pembrolizumab) solution for infusion must be diluted prior to administration. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 (pembrolizumab) to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

Gently invert the bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

> Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

> If a storage temperature excursion is identified, promptly return MK-3475 (pembrolizumab) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact vials is on-going**.**

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. MK-3475 (pembrolizumab) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Route of Administration: IV infusion only. Do not administer as an IV push or bolus injection.

Method of Administration: Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

> Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

Availability

MK-3475 (pembrolizumab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.2 KW-0761 (NSC 791064)

Other Names: Mogamulizumab, AMG 761, POTELIGEO®

Classification: Anti-CC chemokine receptor 4 (CCR4) MAb

Molecular Weight: ~149 kDa

Mode of Action: KW-0761 (mogamulizumab) selectively binds to and blocks the activity of CC

chemokine receptor 4 (CCR4), a G-coupled-protein receptor for C-C chemokines expressed on the surfaces of some types of T cells, endothelial cells, and neurons. KW-0761 (mogamulizumab) is a defucosylated, humanized, IgG1 MAb with lack of fucose resulting in enhanced antibody-dependent cellular cytotoxicity (ADCC) activity. It may induce ADCC against CCR4-positive T cells and inhibit CCR4-mediated signal transduction pathways leading to chemokine-mediated cellular migration and proliferation of T cells, and chemokine-mediated angiogenesis.

How Supplied: KW-0761 (mogamulizumab) is supplied by Kyowa Kirin Pharmaceutical Development, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 20 mg vials containing a sterile, clear, colorless solution (4 mg/mL). KW-0761(mogamulizumab) solution for infusion is formulated in 2.1 mmol/L sodium citrate buffer, 300 mmol/L glycine, and 0.2 mg/mL polysorbate 80 (Tween 80), pH 5.5, supplied in Type I glass vials.

Preparation: KW-0761 (mogamulizumab) solution for infusion must be diluted prior to administration. Do not shake the vials. To prepare the infusion solution add the dose volume of KW-0761(mogamulizumab) to an infusion bag containing 0.9% Sodium Chloride Injection, USP. Non-PVC (polyolefin) IV bags must be used. The final concentration of the infusion solution must be between **0.07 mg/mL to 1.44 mg/mL**.

Storage: Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box.

> If a storage temperature excursion is identified, promptly return KW-0761 (mogamulizumab) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability testing of the intact vials is on-going**.** KW-0761 (mogamulizumab) infusion solutions must be administered within 8 hours of preparation and stored at room temperature.

Route of Administration: Intravenous (IV) infusion

Method of Administration: Infuse over at least 1 hour using an infusion set containing a low-protein binding 0.2 to 0.22 µm in-line filter. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Patient Care Implications: Refer to the protocol for information on evaluation and management of infusion related reactions.

Availability: KW-0761 (mogamulizumab) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application:

https://ctepcore.nci.nih.gov/OAOP/

- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/index.jsp
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biospecimen collections will be performed in accordance with the Schedule of Procedures detailed in the study calendar (Section 10). All specimens should be processed, packaged and shipped according to Section 10 and Appendix C. Memorial Sloan Kettering (PI: Anas Younes, MD) will act as the receiving sites for biomarker specimens as outlined below.

Archival and/or Fresh Tumor Tissue:
Fresh pretreatment (screening) and/**or** archival tumor tissues with sufficient material (25 unstained slides or 2+ tissue blocks) are mandatory for disease confirmation, genomic sequencing, and IHC analysis. However, patients with insufficient biopsy material may still be considered for enrollment on a case by case basis following consultation with the PI.
On-treatment biopsies are mandatory for all patients.
Post-progression biopsies are optional but strongly encouraged for all patients.

Archival tumor samples should be provided in the form of a formalin-fixed paraffin-embedded block. Alternatively, 25 unstained slides (5 micrometers in thickness, on charged, unbaked slides without coverslips) should be provided. Bone metastases, final needle aspirates, cytology specimens and alcohol-fixed specimens are not suitable.

For fresh biopsies, a total of 4 cores should be obtained. 2 cores should be formalin-fixed and paraffin-embedded (FFPE). 2 cores should be snap-frozen in OCT media and shipped on 'dry ice'.

Peripheral blood mononuclear cells (PBMCs):
Serial blood samples will be obtained as per section 10 and Appendix C. PBMCs will be isolated and viably cryopreserved at all time points. Samples are to be shipped on 'dry ice'.

Serum for cytokine analysis:
Serum will be isolated from serial blood samples obtained as per section 10 and Appendix C. Sera will be frozen, shipped on 'dry ice' and stored at -80ºC.

9.1 Integrated and Exploratory Correlative Studies

9.1.1 Targeted genomic sequencing and fluorescence in-situ hybridization of formalin-fixed, paraffin-embedded tumor samples

9.1.1.1 Collection of Specimen(s)
Pre-treatment FFPE biopsy tissue will be obtained and shipped as described in section 9.2

9.1.1.2 Site(s) Performing Correlative Study
DNA extraction from FFPE tissue and next generation sequencing will be performed within MSKCC's Center for Molecular Oncology (CMO). MSK uses a custom, hybridization-based capture panel to detect single nucleotide variants, small indels,

copy number alterations, and structural variants from matched tumor-normal sequence data. Specimens are reviewed by a pathologist to ensure tumor cellularity of at least 10%. Tumors are sequenced to an average unique depth of coverage of approximately 750X. Reads are aligned using BWA, flagged for duplicate read pairs using GATK, and locally realigned using ABRA. Sequence mutations are called using MuTect and reported for >5% allele frequency (novel variants) or >2% allele frequency (recurrent hotspots). Copy number alterations are called using a custom pipeline and reported for fold-change >2. Structural rearrangements are called using Delly. All somatic mutations are reported without regard to biological function.

9.1.2 Immunohistochemical analysis of the tumor and tumor microenvironment

9.1.2.1 Collection of Specimen(s)
Pre-treatment and on-treatment FFPE biopsy tissue will be obtained and shipped as described in section 9.2

9.1.2.2 Site(s) Performing Correlative Study
Immunostaining of FFPE sections from pre-treatment biopsies will be performed as previously described under supervision of the Hematopathology Service in the Department of Pathology. All targets have been validated and successfully used in patients with lymphoma (Vardhana et al, Blood 2016). Expression of MHC-I, MHC-II, and CD58 will be scored in a binary fashion (positive vs. negative) while CD3, CD4, CD8, PD-L1, CCR4 and FoxP3 expression will be scored based on percent of total cells that are positive across 15 high-powered fields. Results will be independently corroborated by 2 pathologists.

9.1.3 Immunophenotyping and functional characterization of the circulating immune cells

9.1.3.1 Collection of Specimen(s)
Peripheral blood will be collected, PBMCs will be isolated (as described in Appendix C) and shipped (as described in section 9.2) at the timepoints described in Section 10.

9.1.3.2 Site(s) Performing Correlative Study
Flow cytometry will be performed within the Immune Monitoring Facility at MSKCC. Flow cytometric assessment of the lymphocyte subsets $CD4^+$, $CD8^+$, $CD16^+$, $CD19^+$ and CD56+ will be examined as percent and absolute number. $FOXP3^+$ and $FOXP3^-$ lymphocytes with the following markers will also include but not limited to: $CD4^+$, CD25, CCR4, CD45RA, CD45RO, LAG3, GARP, PD1, and CTLA4. Activation markers such as CD44 and CD69, will also be examined.

9.1.4 Evaluation of circulating serum cytokines at baseline and in response to therapy

9.1.4.1 Collection of Specimen(s)
Peripheral blood will be collected, serum will be isolated and shipped as described in Appendix C and section 9.2 at the timepoints described in Section 10.

9.1.4.2 Site(s) Performing Correlative Study
Cytokine measurements will be performed on serum by the Immune Monitoring Facility using a Human Th1/Th2/Th17 cytometric bead array (BD Biosciences). Cytokines measured will include IL-2, IL-4, IL-6, IL-10, TNF-a, IFN-g, and IL-17a.

9.2 Collection, Handling and Shipping of biomarker specimens to sites performing correlative studies

Required Specimen	**Collection Time Point**	**Ship To**
Pre-treatment and on-treatment biopsy specimens (B01) 25 unstained slides or 2+ tissue blocks	As per Section 10 *Pre-treatment biopsy is mandatory if adequate archival tissue is unavailable. However, patients with insufficient biopsy material may still be considered for enrollment on a case by case basis following consultation with the PI.*	Memorial Sloan Kettering Cancer Center ATTN: Santosha Vardhana 430 E 67th Street, RRL-469 New York, NY, 10021 646-888-3285
Archival tumor specimen (B02)	As per section 10 *Not required if* B01*is submitted*	Memorial Sloan Kettering Cancer Center ATTN: Santosha Vardhana 430 E 67th Street, RRL-469 New York, NY, 10021 646-888-3285
On-treatment biopsy specimens (B01) – 4 cores 2 cores should be formalin-fixed and paraffin-embedded (FFPE). 2 cores should be snap-frozen in OCT media – send on 'dry ice'	As per Section 10	Memorial Sloan Kettering Cancer Center ATTN: Santosha Vardhana 430 E 67th Street, RRL-469 New York, NY, 10021 646-888-3285

Peripheral blood mononuclear cells (PBMC-01, PBMC-02…) 6 mL of blood per CPT tube x 2 tubes. Process prior to shipping as per Appendix C. Send on 'dry-ice'	As per section 10.	Memorial Sloan Kettering Cancer Center Hematologic Oncology Tissue Bank (HOTB) ATTN: Annie Slingerland 408 E 69th Street, Z-2013 New York, NY, 10021 646-888-3227 PI: James Young
Peripheral blood serum (S-01, S-02…) 6 mL of blood per SST tube x 1 tubes. Process prior to shipping as per Appendix C. Send on 'dry ice'	As per section 10.	Memorial Sloan Kettering Cancer Center Hematologic Oncology Tissue Bank (HOTB) ATTN: Annie Slingerland 408 E 69th Street, Z-2013 New York, NY, 10021 646-888-3227 PI: James Young

9.3 Shipping

All samples will be labeled with the following elements prior to shipping. FFPE samples should be sent in room temerature. All other samples should be shipped on dry ice. Prior to shipping samples, please email MSKCC HOTB (zzPDL_SKI_Hematology_HOTB_Lab@mskcc.org) and Dr. Vardhana (vardhans@mskcc.org) with sample manifest and shipment tracking number (if available).

- NCI 10106
- Study ID
- Time point
- Date collected
- Sample type

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. Laboratory assessments on study should be completed +/- 2 days from treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C4-C34 D1	Off Treatment[j]
Windows			±2d	±2d	±2d	±2d	±2d	±2d	±2d	
MK-3475 (Pemrolizumab)		A			A			A	A	
KW-0761 (Mogamulizumab)		B	B	B	B			B	B	
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X			X			X	X	
Physical exam	X	X			X			X	X	X
Vital signs	X	X			X			X	X	X
Height	X									
Weight	X	X			X			X	X	X
Performance status	X	X			X			X	X	X
CBC w/differential	X	X	X	X	X	X	X	X	X	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X
TFTs (TSH, T3, FT4)[b]	X	X			X				X	X
EKG[c]	X	X	X	X	X			X	X	
Pulmonary Function Test[d]	X									
Adverse event evaluation		X	X	X	X	X	X	X	X	X
Tumor assessments (CT CAP ±PET and)[e]	X							X	X[e]	
B-HCG[f]	X									
Fresh Pre-Treatment Biopsy[g]	X									
On-Treatment Biopsy[h]				X						
Immune cell phenotyping[i]		X			X				X	X
Serum cytokine assessment[i]		X			X				X	X

A: MK-3475 (Pembrolizumab): 200mg IV on Day 1 of a 21-day cycle
B: KW-0761 (Mogamulizumab): For all Phase 1 patients and Phase II Group 1 patients: Dose as assigned; weekly for first 3 weeks (C1D1, C1D8, C1D15) and then once every 3 weeks (C2D1, C3D1, etc.)
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, uric acid. potassium, total protein, SGOT [AST], SGPT [ALT], sodium (to be completed +/- 2 days from treatment).
b: Thyroid function tests. Patients receiving MK-3475 (Pembrolizumab) should be monitored for changes in thyroid function (at screening, periodically during treatment, post-treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
c: Pre and post mogamulizumab infusion EKG will be performed every 3 cycles from C4 onward (C4, C7, C10, etc).
d: If prior history of chemotherapy or radiation therapy induced pulmonary toxicity.
e: Tumor measurements by CT CAP with contrast are initially performed after 2 cycles (6 weeks +/- 7 days) and after every 3rd cycles of treatment thereafter (i.e. every 9 weeks +/- 7 days from the end of C5). PET is required at baseline, after C2 and EOT. Documentation (radiologic) must be provided for patients removed from study for progressive disease.
f: Serum pregnancy test (women of childbearing potential).
g: Archived formalin fixed paraffin embedded (FFPE) tissue (25+ unstained slides or 2 tissue blocks) or Pre-Treatment biopsy specimen (4 cores, allocated as per section 9). For patients with insufficient archival material, a pre-treatment biopsy is requested, however, patients may still be considered for enrollment on a case by case basis following consultation with the PI.
h: Mandatory on-treatment biopsy, Window:C1 D15-21 (4 cores, allocated as per section 9)
i: Peripheral blood samples on C1D1, C2D1, C4D1, C6D1, and EOT: 3 tubes from which PBMCs and serum will be extracted

and stored. j. Off treatment visit will be done 4 weeks ± 3 days from the last treament.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of the phase I part of the study, patients with measurable disease will be assessed by standard criteria.

All patients in the phase II portion of the study will be assessed by standard criteria.

For the purposes of this study, patients should be re-evaluated initially after 2 cycles of treatment (after 6 weeks) and then after every 3 cycles of treatment (every 9 weeks).

11.1 Antitumor Effect – Solid Tumors

The response criteria developed by "The Lugano Classification" for response assessment in lymphoma will be used to define complete response, partial response, and progression of disease in this study. (Cheson et al., 2014) Definitions are detailed in the table below.

Table 3. Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

A new response category called "indeterminate response" (IR) was developed based upon experience with checkpoint blockade therapy in which response assessment may be confounded by the delayed effect of these drugs, allowing for early tumor growth, or therapeutic immune activation that can manifest as growth of existing lesions or development of new lesions, resulting in delayed response or pseudo-progression.(Cheson et al. 2016)

A subject will be considered to have IR in 1 or more of the 3 following circumstances:

1. Increase in overall tumor burden (as assessed by sum of the product of the diameters [SPD]) of ≥50% of up to 6 measurable lesions in the first 12 weeks of therapy.
2. Appearance of new lesions or growth of one of more existing lesion(s) ≥50% at any time during treatment; occurring in the context of lack of overall progression (<50% increase) of overall tumor burden, as measured by SPD of up to 6 lesions at any time during the treatment.
3. Increase in FDG uptake of 1 or more lesion(s) without a concomitant increase in lesion size or number.

As detailed in section "treatment beyond progression," if radiologic imaging shows IR, tumor assessment may be repeated by the site ≥4 weeks later with the option of continuing treatment while awaiting clarification of response.

Progression free survival (PFS) will be calculated from the time of initiation of therapy.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

Enrollment to the Phase 2 portion of this trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user

must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

For studies assigned for ***CTMS Comprehensive*** *Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less

than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually*

Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

13.1.1 Primary Objectives

13.1.1.1 For phase I, to determine the MTD or RP2D of KW-0761 (mogamulizumab) when administered in combination with MK-3475 (pembrolizumab) in patients with relapsed, refractory lymphomas.

13.1.1.2 For phase I, to assess the safety and tolerability of KW-0761 (mogamulizumab) when administered in combination with MK-3475 (pembrolizumab) in patients with relapsed, refractory lymphomas.

13.1.1.3 For phase II, to assess the progression-free survival of KW-0761 (mogamulizumab) when administered in combination with MK-3475 (pembrolizumab) compared to MK-3475 (pembrolizumab) alone in patients with relapsed and refractory diffuse large B-cell lymphomas.

13.1.2 Statistical Considerations for Primary Objectives

The primary endpoint for the phase I portion is to determine the MTD or RP2D of KW-0761 (mogamulizumab) in combination with MK-3475 (pembrolizumab). A standard 3+3 design will be used to find the MTD or RP2D for the combination of MK-3475 (pembrolizumab) and KW-0761 (mogamulizumab). Three patients will be treated at dose level 1. If none or one of the initial 3 patients experience DLT by the end of cycle 1, 3 additional patients will be treated at the same dose level. If none or one of the 6 patients treated at dose level 1 experience DLT, it will be declared as the MTD. If more than one of the initial 3 or the 6 patients treated at dose level 1 experience DLT, dose level will be de-escalated to -1. The same procedure will be carried out at dose level -1. If none or one of the 6 patients treated at dose level -1 experience DLT, it will be declared as the MTD. If more than one of the first 3 or the 6 patients treated at dose level -1 experience DLT, the study will stop and other potential dose levels will be considered.

Escalation will continue only if there is no additional DLT observed. If 2 or more patients experience DLT at any dose level, the previous dose will be declared the MTD. Should 2 or more patients experience DLT at dose level 1, the study will stop and the treatment regime will be re-evaluated. If only 3 patients are treated at a dose declared to be the MTD, 3 additional patients will be enrolled and treated at that dose to confirm the MTD. Therefore, at the completion of the phase I portion, 6 patients will have been treated at the MTD. The target probability of DLT for this regimen is 15%. Patients who withdraw before completing the 4 weekly treatments of KW-0761 (mogamulizumab) for reasons other than development of a DLT will be replaced.

The primary endpoint for the phase II portion is progression-free survival. Patients will be randomized to either MK-3475 (pembrolizumab) plus KW-0761 (mogamulizumab) group or MK-3475 (pembrolizumab) alone group at 1:1 ratio. We assume the 12-month PFS rate is 30% and 10% for the combination and MK-3475 (pembrolizumab)-alone group, respectively. With a

one-sided log-rank test assuming proportional hazards and administrative censoring only, a total of 58 patients (29 per group) will be need to provide 80% power and 0.1 type-I error rate. The expected total number of progression or death events is 45.

To protect patients from exposing patients to unacceptable rate of toxicity, a toxicity-based stopping rule will be applied.

For 30% unacceptable toxicity rate, stop recruitment if ≥5 toxicity events (grade 4 or higher serious adverse events) in the first 15 patients or ≥7 toxicity events (grade 4 or higher serious adverse events) in the 29 patients in each arm.This stopping rule has the following operating characteristics:

True toxicity rate: 0.1, 0.14, 0.18, 0.22, 0.26, 0.30

Probability of stopping recruiting: 0.091, 0.256, 0.472. 0.675, 0.826, 0.919

To protect patients from exposing to potentially non-efficacious treatment, an interim futility as well as efficacy analysis will be performed when half of the expected number of events has occurred. We will consider stopping the trial for futility if the hazard of progression/death (estimated by Kaplan-Meier method) is lower in the MK-3475 (pembrolizumab)-alone group than in the combination group. This futility rule gives 50% chance of stopping the trial early when the combination treatment is no better than MK-3475 (pembrolizumab) alone. (Wieand et al. 1994) We will also stop the trial for efficacy if the one-sided logrank test comparing the two groups using the first half of the sample size gives a p value <=0.0025, which provides strong evidence for the superiority of the combo treatment.

The patients with relapsed, refractory diffuse large B-cell lymphoma treated at MTD in the phase I will be included in the combination group of the phase II portion. Patients withdrawn from the study or lost to follow-up before 12 months will be counted as events. Patients randomized to the MK-3475 (pembrolizumab)-alone group will be allowed to cross-over to the combo group after they progress on the treatment.

Of note, for patients who progress on MK-3475 (pembrolizumab)-alone arm, cross-over to the combination will be allowed.

Progression-free survival (PFS) is defined as the time from C1D1 to the first date of recurrence, progression, or death due to any cause, whichever comes first. Patients who are alive, without evidence of disease will be censored at the date of last follow-up. The Kaplan Meier method will be used to estimate the median PFS.

13.2 Sample Size/Accrual Rate

Proposed Sample Size Minimum: 70 Maximum: 76

Projected accrual rate is 2 patients per month. Thus total accrual will occur over approximately 3

years.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	2	2	2	2	**8**
Native Hawaiian or Other Pacific Islander	1	1	1	1	**4**
Black or African American	6	6	2	2	**16**
White	15	15	4	4	**38**
More Than One Race	3	3	2	2	**10**
Total	**27**	**27**	**11**	**11**	**76**

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13.3 Stratification Factors

N/A

13.4 Analysis of Secondary Endpoints

13.4.1 Secondary Objectives

13.4.1.1 To assess the overall response rate (ORR), complete response rate, partial response rate, and duration of response of KW-0761 (mogamulizumab) and MK-3475 (pembrolizumab) compared to MK-3475 (pembrolizumab) alone in patients with relapsed and refractory diffuse large B-cell lymphomas.

The ORR, CR, and PR rates will be calculated along with exact 95% confidence intervals. The duration of response will be summarized by Kaplan-Meier method in patients who achieve CR or PR.

Exploratory Correlative Analysis

Correlative studies will be performed and summarized using descriptive statistics and graphical displays at pre and post treatment time points.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab).

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.).

However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers, and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drugs, KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab). This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab).** This clinical trial is sponsored by the NCI. **KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab)** may interact with drugs that are ***[processed by your liver, or use certain transport proteins in your body or affects the electrical activity of your heart]***. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX C PBMC ISOLATION PROCEDURE

Objective and Scope:

This procedure describes viable freezing and thawing procedure for blood and marrow mononuclear cells (MNCs), snap freezing (nonviable) and thawing of granulocytes, and freezing/thawing of plasma and serum. All activities will be performed at the site of collection under clean and sterile conditions as indicated, and sent to the Hematologic Oncology Tissue Bank on 'dry ice' for short-term storage prior to correlative studies.

Materials and Reagents:

1. RPMI 1640, Media Lab SKI
2. 25% Human Serum Albumin, Alpine Biologics, NDC 63546-251-05, pharmaceutical grade
3. Dimethyl sulfoxide (DMSO), cell-culture grade (Fisher EC 200-664-3 or similar). Store at room temperature. DMSO must be fresh and sterility maintained. Reagent may be aliquoted in small amounts to help preserve sterility. Certificate of Analysis is provided with each lot and maintained on file.
4. HyClone Trypan Blue Solution, 0.2µm filtered (ThermoScientific SV30084.01); or 0.4% Trypan Blue Solution (Sigma). Store at room temperature. Observe manufacturer's expiration date.
5. Hemacytometer and cover slip
6. Sterile 50ml polypropylene tubes
7. Sterile freezing vials, 1-2ml capacity (e.g., Sarstedt, Nalgene, Nunc) all graded for liquid N2 storage.
8. Alcohol 70% and/or 70% alcohol prep pads
9. Sterile serological pipets
10. Freezer box suitable for –80ºC and/or liquid N2
11. Water Bath
12. Refrigerated and room temperature preparatory centrifuges
13. Controlled rate freezer for subsequent liquid N2 storage
14. Alcohol- and freeze-resistant marking pen
15. Normal pooled or autologous human serum and/or plasma, or fetal calf serum (FCS), depending on the particular needs/uses of a given investigator for the thawed cells.

Procedures:

Freezing Procedure for VIABLE cryopreservation (applies only to marrow and blood MNCs and their subsets.

1. Prepare "Freezing Medium A" for initial resuspension of cells by diluting 100mL of 25% HSA in 100mL RPMI for final 12.5% HSA. NOTE that Freezing Medium A does NOT contain any DMSO. You may scale up or down for different total final volumes.
2. Prepare "Freezing Medium B" by diluting 40mL DMSO, 100mL of 25% HSA stock, and 60mL RPMI. This gives a final volume of 200mL and final concentration of 20% DMSO

and 12.5% HSA. Again, you may scale up or down for different total final volumes.

3. Count viable cells to be frozen using trypan blue exclusion.
4. Final cell concentrations for freezing are as follows, but initial suspensions will be 2x (in Freezing Medium A – see below table), to which an equal volume of Freezing Medium B will be added, after which the final correct concentration is achieved.

Sample Type	Treatment	Total Viable Cell Number	Number of Vials
Mononuclear cells from the Ficoll interface (*blood OR marrow)*	Isolated by density gradient centrifugation & viably cryopreserved in 10% DMSO (final).	≥5x10^6 cells	1-10 vials: Maximum of 10 vials at 5-30 (preferred; max 50) x10^6 final per mL per vial
		<5x10^6 cells	1 vial at 2.5-5 x10^6 final per mL per vial; anything <2.5 x 10^6, min final volume should be 500uL
Blastic acute leukemia, newly diagnosed or relapsed (consider predominantly CD34+ based on %blasts on differential)	Isolated by density gradient centrifugation & viably cryopreserved in 10% DMSO (final).	≥1-10x10^6 blasts	No maximum # vials, each vial at 1-10 x10^6 final per mL per vial;
		<1x10^6 blasts	1 vial at 0.5-1 x10^6 final per mL per vial; anything <0.5 x 10^6, min final volume should be 500uL
Granulocytes (PMNs)	Contained within RBC pellet after gradient centrifugation	N/A because pellet will be snap frozen with or without RBC lysis for eventual recovery of DNA from this WBC source	Eyeball pellet, resuspend in small volume, and divide among vials. No cell count. Put immediately in -80 freezer (no controlled rate, no liquid N2 storage).
Plasma	Isolated from above the MNC interface after density gradient centrifugation of anticoagulated whole blood	N/A	No less than (2) 1 mL aliquots; Maximum (4) 1 mL aliquots
Sera	Isolated by direct centrifugation of clotted whole blood. density gradient separation	N/A	No less than (2) 1 mL aliquots; Maximum (4) 1 mL aliquots

5. Determine the number of vials needed and label freezing vials with the following elements as per section 9.2:
    a. NCI 10106
    b. Study ID
    c. Time point
    d. Date collected
    e. Sample type

6. Place vials to be frozen in -80oC REVCO for 20-30 mins.
7. Also place DMSO-containing freezing medium as well as the medium for resuspending the cells on ice for a minimum of 10 minutes.
8. Remove freezing vials from the –80oC freezer, but keep vials cold.
9. Resuspend viable cells in the "Freezing Media A" (12.5% HSA/RPMI solution, NO DMSO) at HALF the final volume determined by cell concentration, which would be TWICE the desired final cell concentration per mL .
10. To this 2x cell suspension, add an equal volume of the DMSO containing freezing medium (Freezing Medium B), dropwise, while swirling the tube of cells continuously. This gives a 1:1 ratio of Freezing Media A and B. The final concentration is 10% DMSO and 12.5% HSA. The reaction is exothermic, so it is imperative to keep all vials and materials cold.
11. Aliquot this cell suspension in vials.
12. Work quickly to avoid prolonged exposure of cells to DMSO before freezing.

Place labeled vials in controlled rate freezer. Proceed with controlled rate freezing and transfer to vapor phase liquid N2 for storage.

Thawing Procedure for VIABLE recovery (applies only to marrow and blood MNCs and their subsets.

1. Prepare 5-10% normal human plasma or serum/RPMI. Individual investigators may alternatively elect to use FCS instead, depending on their subsequent uses and needs for these cells. For any clinical use of these cells or their progeny, you should use AUTOLOGOUS plasma or serum.
2. Place 10ml of 5-10% plasma/serum RPMI into a 15 mL polypropylene tube and place in waterbath at 37oC for about 30 minutes.
3. Remove vial(s) to be thawed and place directly on dry ice.
4. As it is imperative to thaw rapidly to avoid development of intracellular ice crystals, which will rupture and lyse the cells, and to work quickly so as not expose thawed cells too long to DMSO, it is best to thaw no more than 2 cryovials at a time.
5. Place cryovials into waterbath, shaking continuously and ensuring the lid is not submerged. Thaw until approximately half of the medium in the vial is liquid.
6. Dry off outside and open vial under hood using alcohol wipe at same time
7. Place thawing contents of 1 mL vial into 15ml polypropylene tube with 10ml warm RPMI. Optional rinse of the cryovial and transfer of additional contents to the same polyproylene tube.
8. Spin for 10 minutes at 330 x g in the room temperature centrifuge. Optional additional wash(es) x 1-2 are recommended if nonspecific cell loss will not compromise cell yield needed.
9. After centrifugation and optional wash(es) remove supernatant.
10. Resuspend.

Snap Freezing PMNs/granulocytes (NOT viably cryopreserved):

PMNs/granulocytes sediment with the RBCs in a pellet below Ficoll after density centrifugation. Aspirate off Ficoll. Pellet will be snap frozen with or without RBC lysis for eventual recovery of DNA from this WBC source. Eyeball pellet, resuspend in small volume of RPMI or comparable medium, and divide among vials. No cell count. Put immediately in -80 freezer (no controlled

rate, no liquid N2 storage)

Thawing frozen PMNs/granulocytes:
No special instructions. Thaw at RT or in water bath. Normally used as a source of DNA from WBCs.

Freezing Plasma or Serum:
Aliquot 1mL/vial, no less than 2 vials, max 4 vials.

Thawing Plasma or Serum:
No special instructions. Thaw at RT or in water bath.