A Phase I/II Study of the Safety, Tolerability, and Immunoregulatory Activity of Mogamulizumab (KW-0761) in Subjects with Advanced and/or Metastatic Solid Tumors

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:

A Phase I/II Study of the Safety, Tolerability, and Immunoregulatory Activity of Mogamulizumab (KW-0761) in Subjects with Advanced and/or Metastatic Solid Tumors

Name of Investigational Product:

Mogamulizumab (KW-0761)

Clinical Phase:

Phase I/II

Study Center(s):

Single US center

Study period (months):

Core Study: 18 months (phase I: 6 months; phase II: 12 months)

Long term follow up for phase II study: 24 months

Estimated date first subject screened:03/01/2014

Estimated date last subject completed: 09/01/2015

Objectives:

Primary:

- Determine safety and tolerability profiles, maximum tolerated dose (MTD) if achieved, recommended Phase II dose, and dose-limiting toxicity (DLT) of KW-0761 (Phase I).
- Determine the safety and preliminary efficacy of KW-0761 as determined by immune-related response criteria (irRC) in subjects with triple-negative breast cancer, non-small cell lung cancer, and gastric adenocarcinoma (Phase II).

Secondary:

- Explore the antitumor activity of KW-0761using measures of activity including Best Overall Response Rate (BORR), Disease Control Rate, Duration of Response, Time to Response, and Progression Free Survival (PFS) using and RECIST v1.1 in cohorts of three specific tumor types treated at the MTD.
- Evaluate the effect of KW-0761 on peripheral and intratumoral lymphocyte subset composition and function.
- Evaluate the effect of KW-0761 on long-term safety.

Exploratory:

- Evaluate the impact of KW-0761 on the resident lymphocytes of the skin.
- Evaluate the effect of KW-0761 on the fecal microbiota
- Evaluate KW-0761 dose-response relationships

Methodology:

This is a Phase I/II study of KW-0761 in patients with advanced and/or metastatic solid organ malignancies. Phase I of the study will be an open label, non-randomized, dose escalation, and safety study in adults with histologically confirmed advanced and/or metastatic solid tumor malignancies. Subjects who sign an Informed Consent form and who meet the eligibility criteria will be enrolled to receive a weekly intravenous (IV) dose of KW-0761 ranging from 0.5 mg/kg to 10.0 mg/kg as feasible starting on Day 1 for 4 weeks (cycle 1) and a dose every 2 weeks for 4 weeks starting on day 29 (cycle 2). The initial treatment course will include Cycle 1 + Cycle 2. Subsequent treatment courses are permissible for subjects demonstrating a response or maintaining stable disease and will consist of an infusion of KW-0761 every other week. In the absence of toxicity or progression of disease, patients may stay on study for up to 12 months. If a subject discontinues from the study for reasons other than DLT prior to receiving four complete infusions (Week 4), the subject will be replaced.

	Treatment Course 1						**Subsequent Treatment Courses**	
	Cycle 1				**Cycle 2**		**Cycle**	
Cycle Day	1	8	15	22	1	15	1	15
Study Day	1	8	15	22	29	44		
Study Week	1	2	3	4	5	7		

Standard 3+3 cohorts for safety and DLT detection will be utilized. Each cohort will consist of at least three evaluable subjects. If DLT is observed in 0/3 subjects, escalation to the next dose level will occur. If DLT is detected in 1 of 3 subjects, then three more subjects will be added at that dose level. If DLT is demonstrated in an additional subject, dose escalation will cease. The dose will depend on the cohort in which they have been enrolled. Subjects will be assigned sequentially to a cohort in the order screening is completed. No effort will be made to stratify types of subjects into a particular cohort (e.g., reserve more severe subjects or tumor distribution patterns for the higher doses). Cohorts will be dosed consecutively by ascending dose amount starting with the lowest dose and not in parallel.Telephonic assessments or medical record reviews will occur at Months 6,

12, 18, and 24 after last dose is administered. The Investigator can elect to conduct additional tests and/or follow-up visits in clinic during this period as needed to evaluate and/or treat any adverse event (AEs).

Part 2 of the study (Phase II) will enroll a total of 48 subjects, 16 patients in 3 tumor-specific expansion cohorts each treated with the MTD (or highest dose tested) as determined in the Phase I part of the study. The 3 tumor-specific expansion cohorts will include non-small cell lung cancer, gastric adenocarcinoma, and triple-negative breast carcinoma (negative for immunohistochemical expression of the estrogen receptor, progesterone receptor, and the Her2 protein).

Number of subjects:

Enrollment of up to 72 subjects is planned. Of the 72 subjects, a maximum of 24 will be enrolled in the dose escalation part of this study and the remaining 48 will be enrolled to 3 tumor-specific expansion cohorts. Depending on the dose escalation cohort, 2 to 5 additional subjects may be added to a cohort in whom a dose limiting toxicity has been observed to confirm results (Toxicity Definitions and Stopping Rules; Section 9.5).

Cohort dose schedule:

In the dose escalation portion, the starting dose will be 0.5 mg/kg administered i.v.once every week for four weeks and then once every 2 weeks for 4 weeks. Succeeding dose levels will be 1, 3, and 10 mg/kg as feasible.

Standard 3+3 cohorts for safety and DLT detection will be utilized. Each cohort will consist of at least three subjects. Patients in each cohort must complete the first 4 weeks of study therapy prior to enrollment of subsequent cohorts. If DLT is observed in 0/3 subjects, escalation to the next dose level will occur. If DLT detected in 1 of 3 subjects, then three more subjects will be added at that dose level. If DLT is demonstrated in an additional subject, dose escalation will cease. Cohorts of 3 to 6 subjects will be treated until either DLT, or maximal dose level is achieved. If a subject discontinues from the study for reasons other than DLT prior to receiving four complete infusions (Week 4), the subject will be replaced.

Sequential Cohorts	Dose (mg/kg)
1	0.5
2	1.0
3	3.0
4	10

Definition of Treatment Course

In the first treatment course, KW-0761 will be administered i.v. once a week for four weeks (Cycle 1) and subsequently every 2 weeks for 4 weeks (Cycle 2). Subsequent treatment courses are permissible for subjects demonstrating a response or maintaining stable disease and will consist of an infusion of KW-0761 every other week. Each subsequent course (treatment course 2, treatment course 3, etc.) will be defined as completion of two additional infusions of KW-0761 over 4 weeks. In the absence of progression or toxicity subjects may continue treatment up to one year. If a subject experiences an overall CR, the subject may continue on study for up to an additional four infusions beyond CR, then discontinue treatment in order to determine duration of response. If a subject experiences a PR or SD, the subject may continue therapy after consultation between the investigator and the Principal Investigator until disease progression occurs or other withdrawal criteria are met (refer to Section 4.8, Criteria for Study Termination).

Definition of Maximum Tolerated Dose (MTD)

The MTD is defined as the dose below that dose at which at least 2 of up to 6 subjects in a dosing cohort experience DLT. The MTD will be determined during the first part of this trial.

Definition of Phase II Dose

The Phase II dose will be the MTD as determined in the Phase I part of the trial. If three evaluable subjects do not experience a DLT in the 10 mg/kg dosing cohort then the Phase II dose will be 10 mg/kg.

Dose-Limiting Toxicity

A dose limiting toxicity (DLT) is any toxicity that does not have a clear-cut alternative explanation. Any of the following, specified below, will be considered a DLT:

A DLT will be defined as any $\geq$ Grade 3 non-hematologic or hematologic toxicity that is related to treatment . The following are exceptions to the definition and will be considered a DLT if:

- Grade 4 neutropenia > 7 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding

Dose Escalation

The dose for the first cohort will be 0.5 mg/kg. In the absence of a DLT, dose will be escalated in the following increments, 1, 3, and 10 mg/kg as feasible. Dose escalation will cease when at least one of the following endpoints is reached:

- The MTD is exceeded; OR
- A cohort of at least 3 subjects has been dosed with 10 mg/kg KW-0761

Dose escalation will be based on three subjects receiving four complete infusions of KW-0761.

Replacement of Subjects

During Phase 1, subjects who do not complete the first four infusions for reasons other than a DLT will be replaced.

Phase II

After determination of the recommended dosing level, additional subjects with gastric adenocarcinoma, non-small cell lung carcinoma, and triple-negative breast carcinoma will then be enrolled and treated at that dose. A maximum of 48 subjects, 16 of each carcinoma type are to be treated with the dose determined from the initial portion of the study. A total of 15 subjects, including those receiving the dose determined from Phase 1, will be treated initially.

Criteria for Evaluation:

- **Safety:** The safety of KW-0761 will be determined by reported AEs, changes in physical examinations, vital sign measurements, ECGs and laboratory analyses. Safety evaluations will be performed throughout the study. All AEs and serious AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Scale, Version 4.03. A dose limiting toxicity (DLT) is defined as any Grade 3 or higher infusion reaction or any Grade 3 or 4 toxicity, unless the AE is clearly and incontrovertibly due to extraneous causes.
- **Pharmacodynamics:** A detailed assessment of the biologic activity of KW-0761 will be completed on all subjects enrolled into this study. This will include acquisition of serial serum, peripheral blood mononuclear cells, stool samples, and tumor tissue to evaluate the immunoregulatory activity of this agent.
- **Efficacy:** Efficacy evaluations will be based on response to treatment (PR or better), time to PD and duration of overall response. Changes in tumor measurements and tumor responses will be assessed by the investigator using RECIST 1.1 and irRC .

Statistical Methods

Categorical variables will be summarized using counts and percentages, while continuous variables will be summarized using the mean, median, standard deviation, minimum, maximum, and number of observations. Any statistical testing will be two tailed at the 5% significance level. The frequency of AEs will be tabulated. Baseline, end-of-study, and change from baseline for clinical laboratories, vital signs, and ECG data will be summarized. Descriptive statistics will be computed for safety parameters as appropriate.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives:

- Phase I: Determine safety and tolerability profiles, maximum tolerated dose (MTD) if achieved, recommended Phase II dose (RP2D), and dose-limiting toxicity (DLT) of KW-0761.
- Phase II: Determine the safety and preliminary efficacy of KW-0761 as determined by immune-related response criteria (irRC) in subjects with triple-negative breast cancer, non-small cell lung cancer, and gastric adenocarcinoma.

Secondary Objectives:

- Explore the antitumor activity of KW-0761 using measures of activity; including Best Overall Response Rate (BORR), Disease Control Rate, Duration of Response, Time to Response, and Progression Free Survival (PFS) using both RECIST v1.1 and immune-related response criteria (irRC) in cohorts of three specific tumor types treated at the MTD.
- Evaluate the effect of KW-0761 on peripheral and intratumoral lymphocyte subset composition and function.
- Evaluate the long-term and/or post-treatment safety of KW-0761

Exploratory Objectives:

- Evaluate the effect of KW-0761 on the fecal microbiota.
- Evaluate KW-0761 dose-response relationships.

3.0 BACKGROUND AND RATIONALE

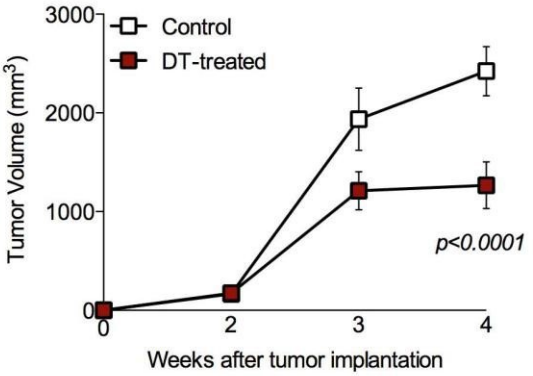


Figure 1. Ablation of Treg cells affects the growth of fully established primary tumors.

A large body of research suggests that the immune system aids in controlling the development of cancer in normal animals by ongoing immune surveillance[1]. Once developed, the tumor microenvironment becomes a site of immune privilege as tumor-specific tolerance has been identified in the absence of generalized immunosuppression[2,3]. As such, immune evasion, resulting from both passive and active tolerizing forces that inhibit antitumor immunity, is a hallmark of cancer [4]. Passive mechanisms include immunoediting, which results in selection for low antigenicity. Active means of tolerization include direct suppression of effector T cells[5]. Regulatory T cells (Treg) are a subset of CD4+ T cells that are requisite for control of autoimmunity, dampening excessive inflammation caused by the immune response to pathogens, and maintaining maternal-fetal tolerance[6-8]. While Treg cells are critical for maintaining peripheral tolerance, their potent immunoregulatory properties can promote the development and progression of numerous types of malignancies by inhibiting effector responses[9,10]. Treg cell recognition of self-antigens is in part responsible for their ability to maintain immune homeostasis. As most tumor associated antigens are modified or aberrantly expressed self antigens, Treg are considered to be active participants in tumor

specific immune privilege[11]. This is particularly exemplified in the observed regression of established tumors in experimental models of Treg cell depletion.[12-14]

Treg cells exert their suppressive function through a number of different mechanisms[10]. CD25, a subunit of the IL-2 receptor and the original Treg cell surface marker, is constitutively and highly expressed on Treg cells but also upregulated on effector T cells[15]. The high level of expression on Treg cells could deprive effector T cells of IL-2 and inhibit their proliferation[16]. CTLA-4 is well known in limiting responses of activated T cells and is also implicated in Treg cell–mediated suppression[17]. Treg cells can also inhibit the function of dendritic cells. LAG-3, a CD4 homologue that exhibits high binding affinity with MHC class II is thought to be required for maximal suppressive action of Treg cells[18]. Binding of major histocompatibility complex (MHC) molecules by LAG-3 on immature dendritic cells (DCs) may lead to inhibition of maturation and decreased costimulatory capacity[19]. Treg cells can produce several suppressive proteins including IL-10, IL-35, granzyme B, IL-9, and TGF-β[20]. Treg cells are capable of killing effector T cells and antigen presenting cells (APC)[21,22]. In a model of infection, Treg cells have also been shown through their influence on DCs to play a critical role in the homeostasis of CD8+ T cell priming by regulating the expansion and avidity of effectors[23].

Treg cells were originally characterized as $CD4^+CD25^+$ lymphocytes and subsequently found to specifically express the forkhead/winged helix family transcription factor Foxp3.[24,25] Treg cell differentiation and function are dependent on the expression of the lineage-specifying transcription factor Foxp3[26]. Furthermore, the entire range of Treg cell functions depends on a Foxp3-dependent hierarchical transcriptional program[27-29]. Mice with a loss-of-function mutation in *Foxp3* lack functional Treg cells and develop lethal autoimmunity and lymphoproliferative disease at an early age[28]. Similarly humans harboring mutations in *FOXP3* suffer from immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)[30]. Expression of Foxp3 drives Treg cell differentiation in the thymus, but they can also be induced in the periphery through mechanisms that involve TGFβ and IL2 [31]. Accumulating evidence demonstrates that Treg cells utilize components of the specific immune response in which they are acting, to suppress it. For example, expression of the transcription factor Irf4 is required for Treg cells to be able to suppress TH2 responses, and Irf4 controls a module of the Foxp3 program that contains 20% of its targets[32]. Similarly, CXCR3, a target of Tbet, is required for control of TH1 responses[33], and Stat3 for TH17 responses[10]. These observations suggest that Treg cells integrate external local cues to modulate specific segments of their transcriptomic programme, and they do so by a set of common regulators they share with the ongoing immune response.

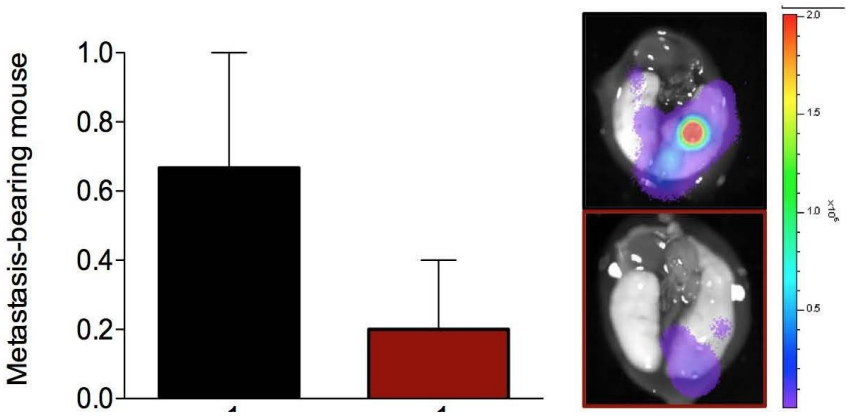


Figure 2. Ablation of Treg cells reduces lung metastasis. Fraction and representative image of mice with detectable lung metastasis upon bioluminescence imaging of the dissected lungs from mice with mammary tumors treated with DT (red) or control (black).

Therapeutic modulation of the immune system for clinical benefit in cancer patients has been demonstrated by numerous modalities including antibody blockade of inhibitory molecules, adoptive T cell transfer, and autologous cell-based vaccines[34-37]. Treg cells are generally considered to be the most potent inhibitor of antitumor immunity and are suspected to be responsible for the limited response rates to current immunotherapeutic regimens[11]. Analysis of tumor infiltrating lymphocyte (TIL) subset composition has shown a clear association between the composition of the infiltrate and patient survival. TIL composed of primarily cytotoxic T cells are generally associated with a favorable prognosis, where as TIL with a predominance of Treg cells correlate with poor outcomes[38-40].

Recruitment of Treg cells into the tumor microenvironment is likely secondary to a number of factors. Chemokines are a superfamily of chemotactic cytokines that control leukocyte migration through G protein-coupled receptors on target cells[41]. The chemokine receptor CCR4 has been shown to be important for trafficking of Treg cells and this function is critical for Treg cell-mediated suppression of inflammation[42]. CCR4 is the receptor for CC-chemokine ligand 17 (CCL17) and CCL22[43]. Chemokines are considered to play a role both in the recruitment of immune and inflammatory cells for anti-tumor response and in the selective homing of neoplastic B and T cells[44]. In normal tissue, CCR4 is known to be selectively expressed on a subset of activated Th2 type $CD4^+$ T cells that produce inflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13, and has garnered attention as a molecular target for the treatment of allergic disorders such as asthma, atopic dermatitis or allergic rhinitis[45-49]. CCR4 is also expressed on primed human Treg cells, activated natural killer (NK) cells, basophils, monocytes, and platelets[50-53]. The CCR4 ligands, CCL17 and CCL22, share 37% homology, are both encoded on chromosome 16, and are highly expressed in the thymus, lymph nodes, and skin, but barely expressed in other tissues[44,54]. MDC and TARC are synthesized mostly by macrophages and dendritic cells[43,47].

CCR4 has been shown to play a central role in Treg homing to the skin where they regulate local immune homeostasis [55]. Reduced levels of skin associated Treg has been found to coexist with numerous immune related skin diseases. Circulating and skin CCR4+ Treg have been shown to be reduced in patients with dermatomyositis [56]. Treg function has been found to be significantly impaired in patients with toxic epidermal

necrolysis [57]. Similarly, administration of Treg has been shown to prevent experimental TEN in mice [58]. Treg may also function to limit skin related autoimmunity as suggested by a reduced homing of functional Treg in patients with vitiligo [59]. Treatment of human subjects with an anti-CCR4 antibody has been shown deplete skin associated Treg, lead to an altered skin immune microenvironment, and potentially be associated with skin immunopathology [60]. The accumulated data regarding Treg mediated immune homeostasis suggests CCR4 to be a major factor in Treg homing to the skin and clinical studies involving interrupting this mechanism should account for this both in monitoring for adverse events as well as a potential biomarker of response.

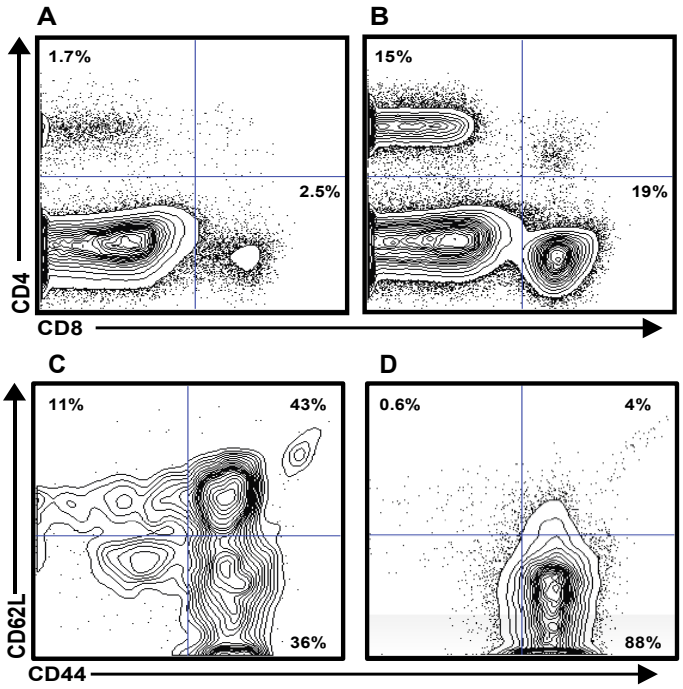


Figure 3. Treg ablation leads to an increased proportion of T cells infiltrating mammary tumors and $CD4^+$ T cell activation. Analysis of TILs from PyMT mammary tumors orthotopically injected in $Foxp3^{DTR}$ mice treated with control (A) or DT (B). Tumor-infiltrating $CD4^+$ T cell expression of activation markers from PyMT mammary tumors orthotopically injected in $Foxp3^{DTR}$ mice treated with control (C) or DT (D).

Accumulation of $CCR4^+$ Treg has been shown to occur in colon adenocarcinomas and correlates with a reduced frequency of effector T cells[61]. Ovarian tumors, Hodgkin lymphoma, and breast cancers are found to contain large amounts of CCL22 that correlates with the presence of tumor infiltrating Treg[40,62-64]. Treg cell migration can be inhibited through CCR4 blockade[65]. Activated Treg cells preferentially express CCR4 over conventional T cells, which is important when considering immunotherapeutic targeting of Treg cells via CCR4[66,67]. A small molecule inhibitor of CCR4 designed in silico has been shown to prevent the interaction of CCL22 and CCL17 with CCR4 and consequently inhibit the recruitment of Treg cells in experimental models[68]. Further work with this molecule showed that CCR4 antagonism could enhance dendritic cell–mediated $CD4^+$ T cell proliferation in vitro as well as offer potent adjuvant activity in an in vivo viral infection model[69]. Similarly, in tumor models, CCR4 antagonism induced expansion of antigen specific $CD8^+$ T cells, and in combination with vaccination, promoted tumor immunity[70].

Excluding skin malignancies, breast cancer is the most common cancer among women and the second leading cause of cancer death in women[71]. Clinically, pathologic evaluation of breast cancer specimens has revealed the prognostic value of certain histopathologic features of breast tumors that reflect alterations in the microenvironment

including lymphocytic infiltration, fibrosis, and angiogenesis. While breast cancer has not traditionally been considered an immunogenic tumor, evidence of tumor infiltrating lymphocytes (TILs) and their subset composition paralleling disease progression suggest that the immune response may be important[72,73]. The clinical relevance of tumor infiltrating T cells has been intensively studied[74]. An increased ratio of CD4+ to CD8+ T cells correlates with lymph node metastases and reduced overall survival[75]. The tumor microenvironment can also influence the recruitment and regulation of immune cells in breast tumors[76,77]. High levels of Treg cells in breast tumors is associated with an invasive phenotype and diminished relapse-free as well as overall survival[57,58,60]. In addition, a substantial decrease in the number of breast tumor infiltrating Treg cells is positively associated with a pathological response to neoadjuvant chemotherapy[56].

Breast cancer is a heterogeneous disease and is generally classified into three basic therapeutic groups, based on the expression of the estrogen receptor (ER), progesterone receptor (PR), and HER2[78]. Triple negative breast cancers (TNBC), also known as basal-like breast cancers lack the expression of ER, PR, and HER2[79]. These tumors account for up to 15% of all invasive breast cancers and are frequently observed in patients with BRCA1 germline mutations and of African ancestry. TNBC characteristically are densely infiltrated by lymphocytes suggestive of an anti-tumor response, yet are associated with a more aggressive clinical course characterized by shorter survival and higher risk of metastases[80]. This paradox is hypothesized to be secondary to effective immune suppression by the tumor microenvironment with preclinical data implicating Treg cells. Foxp3 expression among tumor infiltrating lymphocytes is significantly associated with the TNBC subtype of invasive breast cancers[81]. High levels of Treg cell infiltration of TNBCs is associated shorter survival[82]. TNBC represents a relevant target for immunotherapy as there is a robust pre-existing infiltrate which can potentially mount an anti-tumor response once the Treg cell–mediated immunosuppression is diminished through KW-0761-mediated Treg cell depletion.

The association of Treg cell accumulation in the peripheral blood and tumor infiltrating lymphocytes with clinical outcome is not limited to patients with breast cancer. As Treg cells represent a central mechanism of tumor immune evasion, robust tumor infiltration by Treg cells correlates with poor survival in patients affected by many tumor types. Gastric cancer represents one of the most common causes of cancer-related deaths worldwide[83]. In metastatic gastric cancer, chemotherapy remains the mainstay of therapy and results in objective response rates of only 20-40%, with a median overall survival of 8-10 months[84]. This particularly grim prognosis has led to the investigation of immunotherapy as a means to improve survival[85]. Promising results from initial trials suggest that gastric cancer may be amenable to treatment by modulating the immune system. A clinical trial investigating the use of autologous cytokine-induced killer cells for locally advanced gastric cancer patients showed significant improvements in disease-free and overall survival[86]. A significant amount of preclinical data also suggests that targeting Treg cells in gastric cancer holds therapeutic promise. A study of 133 patients with gastric cancer revealed that high numbers of intratumoral Treg cells significantly correlated presence of lymph node metastases and was an independent factor for adverse overall survival[87]. Regulatory T cells from patients with gastric cancer have also been shown to produce the

immunosuppressive cytokines IL-4 and IL-10, and inhibit cytokine production from CD4+ T cells in vitro[88]. Treg cell infiltration of gastric cancers may be in part related to hypoxia, a feature common to many solid tumors. Treg cell infiltration into gastric cancers is positively correlated with HIF-1α expression and supernatants from gastric cancer cells cultured in hypoxic conditions can induce the expression of Foxp3 in naïve CD4+ T cells via TGF-β1[89]. The well-documented adverse clinical correlation of Treg cell infiltration into gastric cancers, and the preliminary evidence that they may be sensitive to immunotherapy provide the rationale for targeting this disease with KW-0761.

Lung cancer is the leading cause of cancer deaths worldwide. The overall 5-year survival rate for advanced non-small cell lung cancer (NSCLC) is 2%-4%, depending on geographic location[90]. Whereas renal cell carcinoma and melanoma are traditionally considered immunogenic, as evidenced by spontaneous regressions and occasional dramatic responses to high-dose IL-2, NSCLC has been notoriously resistant to immunotherapy[91,92]. Pre-clinical data suggest that the immune system may have a role in this disease. High levels of $CD4^+$/$CD8^+$ T cells infiltrating resected NSCLC tumors are associated with a favorable prognosis and high levels of infiltrating Treg cells are associated with increased risk of relapse[93,94]. In early-stage NSCLC the ratio of Treg cells to CD3+ TILs correlates with disease specific survival and can reliably distinguish patients with tumors who are at high risk for recurrence[95,96]. Genetic evidence pointing to the role of Treg cells in the risk of developing NSCLC was documented by determining the presence of a single nucleotide polymorphism (SNP) associated with Graves disease in a cohort of patients with NSCLC and healthy controls. The study demonstrated a significant association of this SNP with a risk of developing NSCLC[97]. Recently there have been significant breakthroughs in harnessing the immune system though the use of checkpoint blockade inhibitory antibodies to treat NSCLC. In a Phase I dose escalation study of 207 patients treated with an anti-PD-L1 monoclonal antibody, a response rate of 10% was observed in patients with NSCLC[98]. Another Phase I dose-escalation study of 296 patients treated with an anti-PD-1 antibody reported a response rate of 18% in patients with NSCLC[99]. Based on the association of Treg cells with the clinical course of NSCLC patients as well as the significant pool of proof-of-principle clinical data that immune modulation can yield therapeutic responses in this disease, KW-0761 is a promising therapeutic modality for NSCLC patients.

3.1 Preliminary Data

Preliminary data from the laboratory of Dr. Rudensky at the Sloan-Kettering Institute supports the notion that specific ablation of Treg cells is also effective in experimental models of breast cancer. Using a poorly immunogenic, oncogene driven breast cancer cell line in an orthotopic model of mammary carcinoma, we show that Treg cells significantly contribute to breast cancer progression and metastasis. For these studies, we made use of a knock-in mouse generated in our laboratory where the *Foxp3* locus controls expression of the human diphtheria toxin (DT) receptor ($Foxp3^{DTR}$)[100]. In these mice, administration of DT leads to the rapid and specific ablation of Treg cells. Mice expressing a transgene encoding the Polyoma middle T antigen (PyMT) under a mammary gland

specific promoter leads to the rapid development of mammary tumors and lung metastasis faithfully recapitulating human breast cancer carcinogenesis[101]. To determine the role of Treg cells in this process, we orthotopically implanted $1x10^5$ PyMT tumor cells in the inguinal mammary glands of *Foxp3*^{DTR} mice which, when left untreated, developed uniformly growing mammary tumors that metastasized to the lungs with complete penetrance in approximately 3 to 4 weeks. If Treg cells were ablated by injection of 25 µg/kg of DT on 2 consecutive days after tumor reached approximately 100 mm^3, the primary tumor growth of large established tumors was significantly hindered (Fig. 1). In addition, this treatment also resulted in the almost complete disappearance of metastatic tumor nodules in the lungs (Fig. 2). Analysis of TILs by flow cytometry revealed that Treg cell ablation leads to a dramatic increase in the proportion of TILs represented by $CD4^+$ and $CD8^+$ T cells (Fig. 3A,B), as well as an increase in activated $CD4^+$ T cells (Fig. 3B,C). This finding again supports the hypothesis that Treg cells actively suppress potentially beneficial endogenous anti-tumor immune responses.

Unfortunately, there are no readily available means of selectively targeting Treg cells in humans. Preclinical models support the notion that Treg cells are central to the regulation of immune responses to many different types of cancer. Our own preliminary data reveal that the specific ablation of Treg cells in advanced murine breast tumors leads to a significant delay in tumor growth and reduction in metastatic burden. These data suggest targeting Treg cells with KW-0761 may be useful in the treatment of a wide variety of cancers and support its evaluation in this study.

3.2 KW-0761

KW-0761 (also known as AMG 0761 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 Hakko Kirin Pharma, Inc (KHK) for the treatment of T-cell malignancies including peripheral T-cell lymphoma (PTCL), cutaneous T-cell

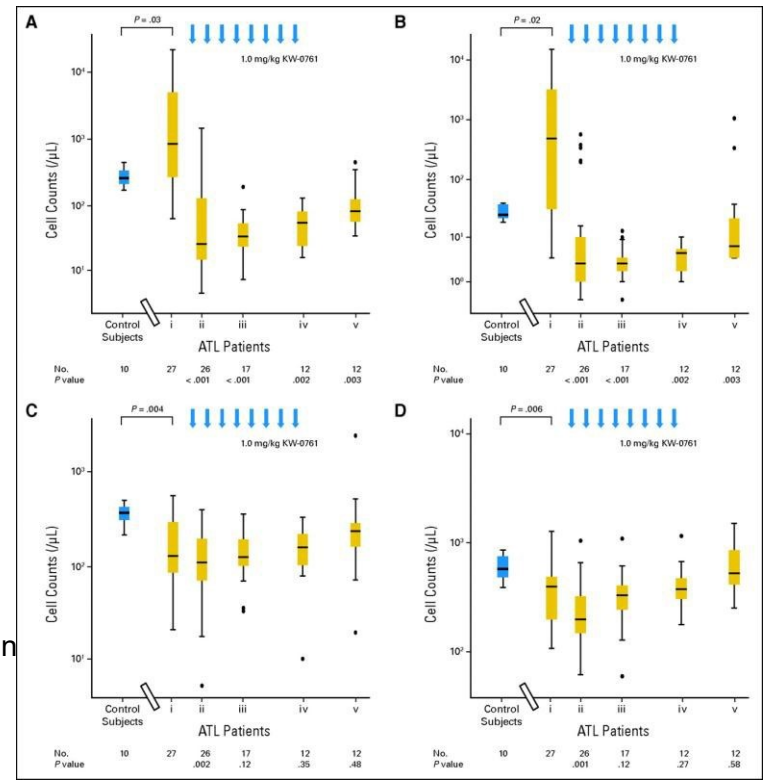


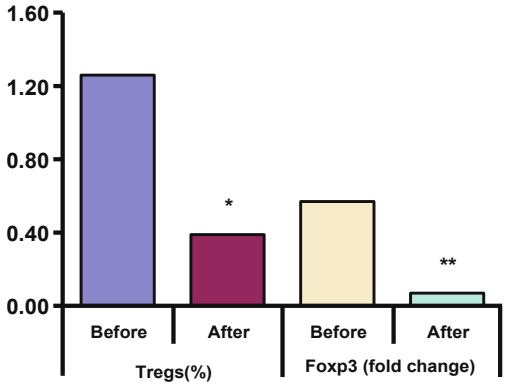
Figure 4. T-cell subset analysis from Phase II clinical trial of KW-0761 for relapsed ATL. (A) Numbers of $CD4^+CCR4^+$ cells from KW-0761–treated patients with ATL in blood samples taken (i) just before the first KW-0761 infusion, (ii) just before the second infusion, (iii) just before the fifth infusion, (iv) 1 week after the eighth infusion, and (v) 4 months after the eighth infusion and those from 10 controls are shown as box and whisker plots indicating minimum, lower quartile, median, upper quartile, and maximum values. The number of samples used for analysis at each point is indicated below the graph. The differences between before and each point after KW-0761 treatment [(i) v (ii), (iii), (iv), or (v)] are indicated as a P value (Wilcoxon signed-rank test) below the graph. Numbers of (B) $CD4^+CD25^+Foxp3^+$; (C) $CD4^+CCR4^-$; and (D) $CD4^-CD8^+$ cells are presented in the same manner.

Amen

lymphoma (CTCL), and adult T-cell leukemia/lymphoma (ATL). KW-0761 was produced using technology developed by Kyowa Hakko Kirin Co., Ltd., that eliminates fucose from the carbohydrate structure of the antibody. It contains 2 heavy and 2 light chains linked together by 16 disulfide bonds. Glycosylation of KW-0761 occurs at amino acid Asn299 and the mAb has typical biantennary structure lacking a core fucose. KW-0761 has a molecular weight of ~149,000 Daltons and an isoelectric point (pI) range of ~8.1 to 8.7. Due to the absence of fucose from the complex-type oligosaccharide at the constant (Fc) region, KW-0761 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. In vitro, the EC50 for ADCC against human T-cell lymphoma cell lines is between 0.01 and 0.1 µg/ml.

KW-0761 has potent cytolytic activity against CCR4-expressing target cells, and has been shown in in vivo non-clinical studies to eliminate the T-helper 2 (Th2) subset of T cells that express this chemokine receptor. When compared to conventional T cells CCR4 is preferentially expressed in Treg, both in mice and humans[66,67]. KW-0761 therefore is a promising immunotherapeutic agent targeting Treg induced immunosuppression in the tumor microenvironment. There is substantial preliminary data in the published work on KW-0761 that suggests it can target Treg. A recently published phase II study of KW-0761 for relapsed ATL showed that compared to healthy controls, KW-0761 led to a significant and lasting decrease in the number of $CD4^+CCR4^+$ but not $CD4^+CCR4^-$ or $CD8^+CD4^-$ cells in patients with ATL (Fig. 4)[102]. Further subset analysis of CD4 T cells showed that there was a significant depletion of $CD4^+CD25^+Foxp3^+$ cells, which included both ATL cells and endogenous non-ATL Treg. The ability of KW-0761 to deplete Treg was also examined in a phase I/II clinical trial in patients with cutaneous T cell-lymphoma (CTCL)[103]. KW-0761 in these patients led to a significant reduction in circulating Treg as well as Foxp3 mRNA as compared to pretreatment levels (Fig 5).

Figure 5. Effect of KW-0761 on Treg in CTCL patients. Fifteen of 20 patients (75.0%) had detectable $CD3^+CD4^+CD25^+CD127^-$ Treg (1.26±1.09 % or 33.79±46.88 /µl) at baseline with 60 –100 % of Treg positive for CCR4. After 4–6 weeks of treatment with KW-0761, all 15 patients had a decrease in Treg numbers (0.39±0.49 % or 5.65±8.95 /µl, *p<0.05). $CCR4^+$ Treg was significantly reduced from an average of 67.2% to 24.6% (p<0.01). In parallel, foxp3 mRNA levels were also significantly decreased from baseline levels (0.57±0.91 to 0.07±0.08, **p<0.01).



In vitro and in vivo pharmacology studies have demonstrated the immunologic and anti-tumor effects of KW-0761. KW-0761 has been examined for safety and toxicology in non-human primates with little toxicity. The No Observed Adverse Effect Level (NOAEL) in a 13 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 preliminary human clinical trials, doses of up to 1.0 mg/kg have been well tolerated. As of 03 December 2012, approximately 243 subjects have received at least one dose of KW-0761 in clinical studies. Efficacy has been demonstrated in subjects with T-cell lymphoma including ATL, CTCL, and PTCL, with overall response rates (ORRs) ranging from 31% to 50%. Adverse events (AEs) have generally been mild to moderate in severity. In three studies in subjects with T-cell lymphoma in the US and Japan, the most frequent treatment-emergent adverse events (TEAEs) that were considered at least possibly related to study drug include infusion related reaction (53%), decreased lymphocyte count (48%), pyrexia (47%), chills (40%), decreased white blood cell count (33%), rash/drug eruption (32%), decreased neutrophil count (28%), decreased platelet count (27%), and nausea (21%). For the 1.0 mg/kg dose level (regimen=once per week for the first 4 weeks then every other week), the mean (SD) half-life values were 184 (64) and 332 (86) hours on Days 1 and 22, respectively.

POTELIGEO® (mogamulizumab) was approved by the Ministry of Health, Labor and Welfare in Japan on 30 March 2012, for the treatment of relapsed or refractory CCR4-positive ATL.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a Phase I/II single institution study. Phase I of the study will be an open label, non-randomized, dose escalation, and safety study in adults with histologically confirmed metastatic solid tumor malignancies. Subjects who sign an Informed Consent form and who meet the eligibility criteria will be enrolled to receive a weekly intravenous (IV) dose of KW-0761 ranging from 0.5 mg/kg to 10.0 mg/kg as feasible starting on Day 1 for 4 weeks. In the absence of toxicity or progression of disease, patients may continue receiving KW-0761 for up to 12 months. Subsequent treatment courses will consist of an infusion every other week (Figure 6). Following the end of treatment or treatment completion date, a 24-week short term follow-up (STFU) period of observation will begin. If a subject discontinues from the study for reasons other than DLT prior to receiving four complete infusions (Week 4), the subject will be replaced. Subsequent treatment courses are permissible for subjects demonstrating a response or maintaining stable disease and will consist of an infusion of KW-0761 every other week.

Subjects will undergo assessments with each dosing visit during Course one and Course 2 and at weeks 2, 3, 6, 12, 18, 24 following the last dose (Figure 6). Telephonic

assessments or medical record reviews will occur at Months 6, 12, 18, and 24 after last dose is administered. The Investigator can elect to conduct additional tests and/or follow-up visits in clinic during this period as needed to evaluate and/or treat any adverse event (AEs).

Phase II of the study will enroll a total of 48 subjects, 16 patients in 3 tumor-specific expansion cohorts each treated at the RP2D (MTD, or highest dose tested in Phase I part of trial). The 3 tumor-specific expansion cohorts will include NSCLC, gastric adenocarcinoma, and triple-negative breast adenocarcinoma (TNBC).

The following definition will be used to identify TNBC subjects:

• <1% immunohistochemical staining for the estrogen receptor AND

• <1% immunohistochemical staining for the progesterone receptor AND

• 0-1+on IHC staining for HER2 or FISH not amplified as per the ASCO/CAP guidelines (single-probe average HER2 copy number <4.0 signals/cell; dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell).

These cohorts were chosen because they are abundantly infiltrated by Treg cells, the proposed target of KW-0761 (Section 3.0, Background and Rationale) [104-106]. As the Phase II part of the study requires specific tumor types there will be no overlap of patients from the Phase I to the Phase II component of the study.

	Screening	Core Study Period						Additional Courses	
		Cycle 1				Cycle 2		Subsequent Cycles	
KW-0761 Injection		Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 15
Study Day	-30 to -1	1	8	15	22	29	44		
Study Week		1	2	3	4	5	7		

Follow-Up									
Short-term (STFU)						Long- Term			
Weeks after End of Treatment/Treatment Completion						Months after STFU/End of Treatment or Treatment Completion			
2	3	6	12	18	24	6	12	18	24

Figure 6. Study Timeline

4.2 Definition of Treatment Course

Amended: 17-AUG-2016

In the first treatment course, KW-0761 will be administered i.v. once a week for four weeks (Cycle 1) and subsequently every 2 weeks for 4 weeks (Cycle 2). Subsequent treatment courses are permissible for subjects demonstrating a response or maintaining stable disease and will consist of an infusion of KW-0761 every other week. Each subsequent course (treatment course 2, treatment course 3, etc.) will be defined as completion of two additional infusions of KW-0761 over 4 weeks. If a subject experiences an overall CR, the subject may continue on study for up to an additional four infusions beyond CR, then discontinue treatment in order to determine duration of response. If a subject experiences a PR or SD, the subject may continue therapy for up to one year or until disease progression occurs or other withdrawal criteria are met (refer to Section 4.8, Criteria for Study Termination). If a subject are not available for administration of KW-0761 a 3 day window before or after the scheduled dose date will be allowed.

4.3 Dose Escalation

Standard 3+3 cohorts for safety and DLT detection will be utilized (Table 1). Each cohort will consist of at least three subjects. If DLT is observed in 0/3 subjects, escalation to the next dose level will occur. If DLT detected in 1 of 3 subjects, then three more subjects will be added at that dose level. If DLT is demonstrated in an additional subject, dose escalation will cease (see Table 6 for a summary). The dose will depend on the cohort in which they have been enrolled. Subjects will be assigned sequentially to a cohort in the order screening is completed. No effort will be made to stratify types of subjects into a particular cohort (e.g., reserve more severe subjects or tumor distribution patterns for the higher doses).

In the absence of progression or toxicity subjects may continue treatment up to one year. If a subject experiences an overall CR, the subject may continue on study for up to an additional four infusions beyond CR, then discontinue treatment in order to determine duration of response. If a subject experiences a PR or SD, the subject may continue therapy after consultation between the investigator and the Principal Investigator until disease progression occurs or other withdrawal criteria are met (refer to Section 4.8, Criteria for Study Termination).

Table 1. Phase I Dose Escalation Schema

Cohort	Dose (mg/kg)
1	0.5
2	1
3	3
4	10

4.4 Study Conduct

Table 2 is a tabular view of the Study Assessments.

Visit 1 is designated as Day 1 and the day of KW-0761 administration. Screening for criteria will begin no more than 30 days prior to KW-0761 dosing on Day 1 with the signing of the ICF. Unless otherwise specified, all screening assessments should be performed during this period. Assessments required for screening eligibility that are already available in a subject's medical records at the time the subject is consented may be used to satisfy screening requirements as long as they have been obtained within 30 days of the planned KW-0761 dosing on Day 1. If screening assessment results for eligibility are not available in a subject's medical record then they must be obtained to establish eligibility. Pathologic review of most recent biopsy for confirmation of diagnosis will be obtained during the screening period. The imaging studies for TNM staging that will be used to establish eligibility and baseline must have been performed within 30 days of KW-0761 dosing. For women of child bearing potential a negative urine pregnancy test must be documented on Day 1 prior to KW-0761 dose administration. Information to be collected during the Long-term Follow-up will include: vital status; treatments received post KW-0761 dosing. This information will be sought first from hospital and/or outpatient medical records. If the subject has not been seen for follow-up care in the 30 days prior to scheduled visit, then a study staff member will contact the subject by telephone to collect information regarding vital status and treatments.

Table 2. Assessments

Procedures	Screening	Treatment Course 1						Subsequent Courses	
		Cycle 1				Cycle 2		Subsequent Cycles	
		Days (+/- 3 days)							
	(-30) to (-1)	1	8	15	22	1	15	1	15
Informed Consent	X								
Entry Criteria	X								
Medical History	X								
Karnofsky Performance Status	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Height	X								
Vital Signs	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X							
Urine Bhcg	X	X							
Serum Chemistry	X	X		X		X			
Urinalysis	X	X							
CBC with Differential	X	X	X	X	X	X	X	X	X
Coagulation profile	X								
Stool Analysis[1]	X	X	X	X	X		X		
Cytokines/Flow Cytometry/ Lymphocyte counts	X	X	X	X	X		X		
CMV Ag and Ab	X								
HIV , Hepatitis panel	X								
Quantitative Immunoglobulins	X				X				
Humoral and cellular responses to tumor antigens	X				X				
Tumor Imaging (CT or MRI scan or equivalent)[3]	X						X		X
AJCC Tumor Staging	X								
Tumor Biopsy[2]	X			X (+ 4 days)					
Mogamulizumab infusion		X	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

[1]Since the bowel habits of individual subjects may vary widely it is likely that not all of the collections may be possible. Subjects are to bring in samples when feasible. If a subject misses collections they will be allowed to continue on the study.

[2]If a site of tumor is readily available as a cutaneous lesion a simple punch or excisional biopsy under local anesthesia can be performed by the principal investigator or qualified personnel. If however tumor is not as readily accessible then an image-guided core needle biopsy will be obtained following consultation with the radiology staff to determine the overall risk of the procedure. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. If a surgical procedure is performed for a clinical indication a sample may be used for research purposes. During the course of treatment a decision may be made to perform the post-treatment biopsy earlier than 15 days if there is evidence to suggest a possibility that by day 15 there will be no available tumor for biopsy due to a rapid clinical response. Similarly tumor biopsy may be delayed if there is evidence of a delayed response.

[3]Tumor imaging will occur on even courses starting with cycle 4.

Procedures	Follow-Up									
	Short-term (STFU)						Long- Term			
	Weeks after End of Treatment or Treatment Completion						Months after STFU/End of Treatment or Treatment Completion			
	2	3	6	12	18	24	6	12	18	24
Karnofsky Performance Status	X	X	X	X	X	X	Telephone assessments or medical record reviews will occur at 6, 12, 18, and 24 months after the end of the Short-term follow up period, the end of treatment or treatment completion date. Vital status, directed AE assessment for new onset or exacerbation of pre-existing autoimmune disease.			
Physical Examination	X	X	X	X	X	X				
Weight				X		X				
Height										
Vital Signs	X	X	X	X	X	X				
CBC with Differential				X		X				
Stool Analysis		X		X		X				
Cytokines/Flow Cytometry/ Lymphocyte counts		X		X	X	X				
Tumor Imaging					X					
AJCC Tumor Staging					X					
Assessment of response					X					
AE assessment	X	X	X	X						
Concomitant Medications	X	X	X	X	X	X				

4.5 Assessments

As shown in Table 2, screening assessments will be performed to determine eligibility. At a minimum, demography, medical and disease history, concurrent and recently taken medications, and laboratory and physical examination results will be reviewed to confirm that a subject is eligible to screen for enrollment. An original medical history including complete past medical and surgical history, review of systems, complete history of present illness for all active medical and surgical problems, and current prescription and non-prescription medications will be recorded.

4.5.1 Vital Signs

Vital signs including temperature, respiratory rate, heart rate, and blood pressure will be recorded at each visit. During Phase 1, vital signs will be checked and recorded prior to administration of KW-0761, every 15 minutes (± 5 minutes) during infusion for the first treatment course and midway through and at the end of the infusion on subsequent treatment courses. Vital signs will also be measured every 30 minutes (± 5 minutes) for the first hour following administration of KW-0761. During Phase 2 of the study, vital signs will be checked and recorded prior to start of infusion and at the end of the infusion.

4.5.2 Physical Examination

Complete physical examinations will be performed at Screening/Baseline to document that candidates meet all eligibility criteria and will be repeated weekly during the core study period and with every short-term follow-up visit. Height will be recorded at Baseline. Weight will be recorded at Baseline, at the end of Cycle 1 and at the end of Cycle 2. Complete examinations include all major organ systems. The Investigator will preferably complete these examinations.

Directed physical examinations can be performed by study staff at other points if deemed necessary by clinical presentation of the subject.

4.5.3 Electrocardiogram (ECG)

A 12-lead ECG will be obtained and recorded at Screening Baseline (Days -35 to -1) and prior to the initial KW-0761dose. Additional ECGs will be obtained only as clinically indicated.

4.5.4 Tumor Imaging for AJCC TNM Staging

Chest, abdominal, pelvic, and CNS imaging scans will be documented at Screening / Baseline to stage subject's tumor according to the American Joint Committee on Cancer Tumor-Node Metastases (AJCC TNM) scoring system. As noted in Section 4.4, the imaging studies used to stage the subject's tumor may have been obtained as part of the subject's routine cancer care prior to study enrollment but must have been obtained within 30 days of KW-0761 dosing on Day 1.

4.5.5 Laboratory Assessments

The following laboratory evaluations at Screening / Baseline and Day1 prior to KW-0761 dosing to document eligibility and establish baseline values.

- Serum creatinine (Cr) ≤1.5 X upper limit of normal (ULN)
- Serum total bilirubin (T-Bil) ≤1.5 X ULN (prior diagnosis or past history consistent with Gilbert's syndrome is an exception)
- Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 X ULN
- Platelets (Plts) ≥ 100,000 cells/µl
- Hemoglobin (Hgb) ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) ≥1000/mm^3

Serum chemistry [including sodium (Na), potassium (K), chloride (Cl), carbon dioxide (C02), albumin (Alb), alkaline phosphatase (ALP), Bil total, aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), total protein (TP), calcium (Ca), creatinine (Cr), phosphorus (Phos), glucose (Glu), and lactate dehydrogenase (LDH)], CBC with differential, and urinalysis (U/A) will be performed prior to KW-0761 dosing. All of these will be repeated as shown in Table 2. Additional laboratory tests will be repeated as needed.

4.5.6 Pregnancy Screen

For women of childbearing potential, urine pregnancy testing will be performed at Screening / Baseline and on Day 1 prior to dosing.

4.5.7 Adverse Events (AE) Assessment

Evaluation of AEs will occur continuously throughout the study. Scheduled safety assessments including AE reporting is shown in Table 2. The definition and reporting of AE are described in Section 9. During Phase 1, subjects who do not complete the first four infusions for reasons other than a DLT will be replaced. Based on the tolerability of KW-0761 in previous trials we expect a very low drop-out rate. If a subject begins a new treatment investigational or otherwise following participation in this study information regarding adverse events will continue to be collected but will not be considered secondary to KW-0761.

4.6 Number of Subjects

Enrollment of up to 72 subjects is planned. Of the 72 subjects a maximum of 24 will be enrolled in the dose escalation part of this study and the remaining 48 will be enrolled to 3 tumor-specific expansion cohorts. Depending on the dose escalation cohort, 2 to 5 additional subjects may be added to a cohort in whom a dose limiting toxicity has been observed to confirm results. During Phase 1, subjects who do not complete the first four infusions for reasons other than a DLT will be replaced.

4.7 Treatment Assignment

After informed consent has been obtained, subjects will be assigned a sequential screening number when screen procedures commence. Subjects are assigned a screening number after signing the informed consent form and prior to conducting any other study-related procedures. Those who withdraw or screen fail after being assigned a screening number will retain that number and the screening number will not be reassigned to another subject. Upon meeting all eligibility requirements and receiving KW-0761, subjects will be assigned a sequential study number. The first subject will be given the number 0001, the second will be 0002, and so on. This subject number will be maintained throughout the study.

Subjects will be enrolled and dosed in sequential cohorts as outlined in the dosing schedule (Table 1). The Principal Investigator will conduct safety monitoring and cohort dosing will proceed conservatively. Prior to initiating dosing, the Investigator will send selected screening data on the Eligibility Checklist to the Principal Investigator for review and approval. Following enrollment of the first (sentinel) subject into a cohort and review of that subject's data through Day 8 (see Section 4.4), the Principal Investigator will determine if additional subjects may be enrolled in that cohort.

Details regarding safety criteria for advancing or stopping subjects are summarized in Section 9.5 and Table 6.

4.8 Criteria for Study Termination

Safety-related Stopping Rules are outlined in Section 9.5. If a Stopping Rule is met, then further enrollment will cease and all available data on all subjects enrolled thus far will be reviewed by the and Principal Investigator to determine if the study should proceed and if so, what changes must be implemented.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 KW-0761

5.1.1 Description

The KW-0761 drug product will be provided as an injectable solution, contained in single-use, ready-to-use 10 mL vials. Each vial contains 5 mL of a 4 mg/mL solution of KW-0761 drug substance in a colorless glass vial with fluoropolymer coated butyl rubber stoppers and polypropylene flipoff cap with aluminum overseal.

5.1.2 Preparation of Dose

The dose and volume of the study drug to be administered will be dependent upon the subject's weight. If the subject's body weight changes 10% or more at any time during the study relative to Day 1, subsequent doses of the study drug should be adjusted relative to the new weight.

The appropriate volume of KW-0761 based on weight will be withdrawn and diluted into normal saline (NS, 0.9% sodium chloride). KW-0761 can be diluted with normal saline to various concentrations ranged (0.07 to 1.44 mg/mL in a 250-mL bag; 0.19 to 2.40 mg/mL in a 500-mL bag; or 0.10 to 1.20 mg/mL in a 1000-mL bag) and stored at 25°C for up to 24 hours to effectively deliver the planned clinical doses. However, since there are no preservatives, it is recommended the product be used within 8 hours. KW-0761 will then be filtered through a 0.22 µm protein-sparing/low-protein binding in-line filter. Refer to the KW-0761 Pharmacy Manual for additional details.

5.2 Study Drug Administration

Subjects will receive KW-0761 as an i.v. infusion over 1 hour for the 0.5 and 1.0 mg/kg dose, 1.5 hours for the 3.0 mg/kg dose and 2 hours for the 10 mg/kg dose. Subjects will be observed closely for 1 hour following each administration of KW-0761 for any potential AEs in an area with resuscitation equipment. During Phase 1, vital signs (including temperature, pulse, respiratory rate, and blood pressure) will be checked and recorded prior to administration of KW-0761, every 15 minutes (± 5 minutes) during infusion for the first treatment course and midway through and at the end of the infusion on subsequent treatment courses. Vital signs will also be measured every 30 minutes (± 5 minutes) for the first hour following administration of KW-0761. During Phase 2 of the study, vital signs will be checked and recorded prior to start of infusion and at the end of the infusion.

KW-0761 should only be administered under the supervision of a qualified physician. Premedication with acetaminophen 650 mg orally and diphenhydramine 50 mg i.v. or other antihistamine will be administered to all subjects. In the event that a subject experiences a grade 1 or 2 hypersensitivity reaction, the KW-0761 administration time may be increased. If this is not effective, removal of the subject from the study should be considered. Should a hypersensitivity reaction to KW-0761 occur, the subject must be treated according to the best available medical practices. Subjects should be instructed to report any delayed reactions to the investigator immediately.

5.3 KW-0761 Formulation and Storage

For this study, KW-0761 is formulated at 20 mg/vial in 2.1 mM sodium citrate buffer, pH 5.5 containing 300 mM glycine, and 0.02% polysorbate 80 (Tween 80). KW-0761 should be stored at a temperature of 2°C to 8°C. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions.

5.4 Packaging and Labeling of KW-0761

KKP will distribute the study drug to the pharmacies at the study site. Vial labels will bear the appropriate text as required by regulatory agencies. At a minimum, the label will include:

- appropriate cautionary statement limiting, by Federal Law, the new drug to investigational use;
- product name (KW-0761)
- drug storage requirements
- lot number

5.5 Drug Accountability

The Principal Investigator and pharmacy at the study site are responsible for maintaining accurate records of the receipt, dispensing, and return of all investigational materials. The Investigator may dispense study drug only to subjects enrolled in the study. All dispensing must be from the site listed in the FDA form 1572. Under no circumstance will the Investigator allow study drug to be used other than as directed by the protocol.

5.6 Return and Destruction

Upon completion or termination of the study, all unopened vials of KW-0761 must be destroyed at the site. Disposal of these containers should occur at the investigational center according to the investigational site's standard chemotherapy or biohazardous waste procedures. It will be the Investigator's responsibility to arrange for disposal of all drug products with containers, provided that procedures for proper disposal have been established according to applicable regulations and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. A copy of the certificate of destruction must be placed in the trial master file. If the institutional site is unable to dispose of the study drug, then KKP should be contacted to arrange for destruction. All KW-0761 returned to should be accompanied by the appropriate documentation and be clearly identified by protocol number on the outermost shipping container. Returned supplies should be in the original containers (i.e., subject study drug containers that have clinical labels attached). Refer to the KW-0761 Pharmacy Manual for additional details.

5.7 KW-0761 Clinical Safety

As of December 03, 2012, approximately 243 study subjects have received at least one dose of KW-0761 (doses of KW-0761 ranging from 0.0001 to 1.0 mg/kg in clinical studies of KW-0761) and safety information is summarized in Investigator's Brochure Edition Number:9 (IB, see Appendix), Section 5.2.1. Pooled treatment emergent adverse events (TEAEs) and serious adverse event (SAE) data considered at least possibly related to study drug for KKP Study KW-0761-001 and KHK Studies 0761-0501 and 0761-002 are summarized in IB Sections 5.2.1 and 5.2.1.1, respectively. Individual study synopses are provided in IB Section 5.2.3.

5.7.1 Safety Summary

The most frequently observed TEAEs (≥ 10% of total subjects) that were considered to be at least possibly related to KW-0761 in completed studies of subjects with T-cell lymphoma in the US and Japan are presented in Table 3. The TEAEs observed have been generally mild to moderate (≤ Grade 2) in severity.

Infusion reaction was the most common TEAE. Most infusion reactions were generally mild to moderate in severity and symptoms (chills, fever, headache, etc.) were similar to what has been observed with other monoclonal antibodies. More subjects in the Japanese studies experienced infusion reactions than in the US, which may be attributable to more frequent and intensive monitoring in the in-patient hospital setting and the way infusion reactions are assessed in Japan.

Skin rashes, including drug eruptions, considered to be at least possibly related to KW-0761 administration have been reported in all studies. In the US Study KW-0761-001 in CTCL/PTCL with a dosing regimen of four weekly doses followed by one dose every other week, 17% of subjects (7 subjects) experienced a study drug related rash, most of which were considered mild or moderate in severity. One subject had a Grade 3 rash. In the Japanese studies, study drug related rashes were observed in 25% of subjects (4 subjects) in the Phase 1 Study 0761-0501 (4 doses given weekly) and 59% of subjects (16 subjects) in the Phase 2 Study 0761-002 (8 doses given weekly). The incidence and severity of the rashes observed in subjects in Japan is notably greater than what has been observed in the study conducted in the US. This may be related to differences in the dosing regimen, differences in underlying biology of the malignancies and/or differences in

Table 3: TEAEs Considered at Least Possibly Related to KW-0761: Oncology Studies KW-0761-001, 0761-001, 0761-0501 and 0761-002

Preferred Term	KW-0761-001 (US) N=42 n (%)	0761-0501 (Japan) N=16 n (%)	0761-002 (Japan) N=27 n (%)	Total N=85 n (%)
Infusion related reaction	8 (19.1)	13 (81.3)	24 (88.9)	45 (52.9)
Lymphocyte count decreased	0	15 (93.8)	26 (96.3)	41 (48.2)
Pyrexia	6 (14.3)	11 (68.8)	23 (85.2)	40 (47.1)
Chills	10 (23.8)	8 (50.0)	16 (59.3)	34 (40.0)
White blood cell count decreased	0	10 (62.5)	18 (66.7)	28 (32.9)
Rash[a]/Drug eruption[b]	7 (16.7)	4 (25.0)	16 (59.3)	27 (31.8)
Neutrophil count decreased	0	10 (62.5)	14 (51.9)	24 (28.2)
Platelet count decreased	0	9 (56.3)	14 (51.9)	23 (27.1)
Nausea	10 (23.8)	3 (18.8)	5 (18.5)	18 (21.2)
Alanine aminotransferase increased	0	5 (31.3)	11 (40.7)	16 (18.8)
Aspartate aminotransferase increased	0	5 (31.3)	10 (37.0)	15 (17.6)
Blood lactate dehydrogenase increased	0	3 (18.8)	10 (37.0)	13 (15.3)
Headache	7 (16.7)	2 (12.5)	3 (11.1)	12 (14.1)
Tachycardia	0	4 (25.0)	8 (29.6)	12 (14.1)
Blood alkaline phosphatase increased	0	5 (31.3)	6 (22.2)	11 (12.9)
Blood pressure increased	2 (4.8)	2 (12.5)	6 (22.2)	10 (11.8)
Haemoglobin decreased	0	1 (6.3)	8 (29.6)	9 (10.6)
Hypoxia[c]	0	4 (25.0)	5 (18.5)	9 (10.6)

a: For Study 0761-002, eczema and eczema nummular are also included in the events presented as rash.
b: For Study KW-0761-001, rash was coded to drug eruption.
c: The adverse events coded to hypoxia represented changes in pulse oximetry readings.

the underlying genetic predispositions (most subjects in Japan had ATL, while all but one in the US had CTCL). In the 0761-002 study, dosing with KW-0761 was not required to be discontinued after the appearance of rash, which was medically treated. In this study the number of doses received was related to both the incidence and grade of the skin rashes. After 4 weekly doses, the incidence of skin rash increased markedly with continued weekly dosing and the most severe skin adverse event experienced by a patient in this study tended to be with the highest number of doses. Cutaneous SAEs, including rash and Stevens- Johnson syndrome that were reported as possibly or probably related to KW-0761 are described in Section 5.7.2.

In the non-oncology studies, one subject in a Phase 1 study in asthma (Study 20080407) developed a Grade 2 psoriasiform rash after receiving a single dose of KW-0761 (0.6 mg) administered subcutaneously.

Most rashes observed in the studies in T-cell lymphomas have been characterized as spongiotic dermatitis, although there has been some variability in presentation. The rash observed in the subject with asthma was characterized as psoriasiform. There is also great variability in the time to onset of rash among subjects. The majority of subjects with ATL and CTCL/PTCL have underlying skin involvement and dysregulated skin immunity as a result of the underlying lymphoma/leukemia. Although the mechanism is unclear in terms of how skin rashes develop in these oncology subjects, rash appears to be manageable by temporarily withdrawing KW-0761 or adding topical and/or oral steroids.

The most common related ≥ Grade 3 laboratory TEAEs included lymphocyte count decreased (35.3%), white blood cell count decreased (11.8%), neutrophil count decreased (9.4%) and platelet count decreased (5.9%). Alterations in lymphocyte counts were anticipated based on the pharmacological activity of KW-0761.

5.7.2 Serious Adverse Events

Forty-six SAEs considered at least possibly related to KW-0761 were reported for 32 subjects. Data are presented for all studies in Table 4.

Several SAEs have been the result of CMV reactivation (chorioretinitis, pneumonia). In Study 0761-003, KW-0761 is given in combination with the chemotherapeutic regimen, mLSG15, in subjects with ATL. Both the chemotherapeutic regimen and the disease itself are immunosuppressive. A recent study demonstrated that subclinical reactivation of CMV was common (50.6%) in ATL patients receiving chemotherapy.[44] Since there is a temporal association between the KW-0761 and chemotherapy infusions, relationship to KW-0761 cannot be ruled out.

One subject in Study 0761-0501 with ATL experienced hepatitis B (HB) reactivation following treatment KW-0761. Blood samples obtained from the subject after the onset of symptoms were positive for hepatitis core antibody. Repeat testing confirmed that HBs antigen and HBs antibody were both negative prior to antibody treatment. The protocol did not require testing for hepatitis B core antibody or HBV-DNA at the time the subject was enrolled in the study. The protocol was subsequently amended to require such testing to prevent HBV activation in other subjects.

One subject in Study 0761-0501 who received 4 weekly infusions of 0.01 mg/kg of KW-0761 experienced herpes zoster on study Day 99. Another subject in Study 0761-004 experienced herpes esophagitis on study Day 68. These subjects did not have a prior history of herpes infection.

Seven subjects in clinical trials experienced SAEs of rash and one subject experienced an SAE of Stevens-Johnson syndrome (SJS) that were reported as possibly or probably related to KW-0761; 7 of these subjects were treated in Japanese studies of KW-0761. SJS was reported for a subject in the Phase 2 ATL study in Japan (0761-002). A 71-year-old woman received 1 mg/kg KW-0761 weekly for 8 weeks and developed a Grade 1 skin eruption suspected of being a drug eruption related to a concomitant medication on Day 21. The skin eruption worsened over a period of several weeks and the subject was hospitalized with SJS on Day 75. It should be noted that the subject was on numerous medications, several of which have been associated with SJS. The subject was treated with ophthalmic, iv and oral steroids, antihistamines, anti-virals and immunoglobulin. As of Day 401, the event was reported as resolving.

Several SAEs have been the result of new onset malignancies. Two subjects with Sézary syndrome in study KW-0761-001, both from the same study site, were reported to have secondary T-cell malignancies that were immunophenotypically distinct T-cell lymphomas, i.e., gene rearrangements different from their initial diagnoses. It is well known, however, that in patients with CTCL, the presence of multiple T-cell clones, although not common, does occur with regularity.

Table 4. Serious Adverse Events at Least Possibly Related to KW-0761 (all studies)

Study Number	Subject ID/ Age/Sex[a]	KW-0761/ AMG 761 Dose	Event Preferred Term	Onset Day	Resolution Day or Outcome	Worst Grade/Intensity
Oncology						
0761-0501	102/60/M	0.01 mg/kg	Herpes zoster	99	106	Severe/Grade 3
	103/68/F	0.01 mg/kg	Hepatitis B	186	486	Severe/Grade 3
	412/62/M	1.0 mg/kg	Rash	26	415	Severe/Grade 3
KW-0761-001	04-02/63/M	1.0 mg/kg	Hypotension	1	2	Mild/Grade 1
			Abdominal pain	1	2	Moderate/Grade 2
			Neoplasm malignant	611[b]	Recovering	Mild/ Grade 1
	04-03/36/F	1.0 mg/kg	Neoplasm malignant	443[c]	Recovering	Mild/ Grade 1
0761-002	0301/71/F	1 mg/kg	Stevens Johnson Syndrome	75	Recovering	Severe/Grade 3
	0312/66/F	1 mg/kg	Rash	33	Recovering	Severe/Grade 3
	0321/57/M	1 mg/kg	Rash	110	343	Severe/Grade 3
	0907/60/M	1 mg/kg	Rash	127	346	Severe/Grade 3
	0918/65/F	1 mg/kg	Rash	41	198	Severe/Grade 3
0761-003[d]	03-02/66/M	1 mg/kg (+mLSG15)	Pneumonitis	96	Recovering	Unknown
			Interstitial lung disease	283	Recovering	Grade 4/Life-threatening
	03-07/65/F	1 mg/kg (+mLSG15)	Pneumonia	110	166	Unknown
			Interstitial lung disease	280	Recovering	Unknown
	05-01/68/M	1 mg/kg (+mLSG15)	Encephalitis viral	117	138	Unknown
	09-03/69/M	1 mg/kg (+mLSG15)	Febrile neutropenia	114	129	Unknown
			Pneumonia	119	Recovering	Unknown
			Pneumonia cytomegaloviral	171	Not recovered	Unknown
	11-01/49/M	1 mg/kg (+mLSG15)	Generalized erythema	36	134	Severe/Grade 3
	13-01/65/F	1 mg/kg (+mLSG15)	Oral disorder	125	173	Severe/Grade 3
	17-01/62/F	1 mg/kg (+mLSG15)	Exfoliative rash	226	342	Unknown
	17-03/54/M	1 mg/kg (+mLSG15)	Cytomegalovirus infection	13	28	Unknown
	19-02/60/F	1 mg/kg (+mLSG15)	Cholecystitis	46	74	Unknown
0761-004	03-22/53/M	1 mg/kg	Cytomegalovirus chorioretinitis	20	Recovering	Unknown
			Pneumonitis	10	Recovering	Unknown
	03-07/52/F	1 mg/kg	Vomiting	35	38	Grade 2
	06-11/65/M	1 mg/kg	Cytomegalovirus chorioretinitis	22	Recovering	Unknown
	06-16/74/M	1 mg/kg	Polymyositis	64	Recovering	Unknown
	07-37/81/F	1 mg/kg	Treatment related secondary malignancy	288	Recovering	Unknown
	08-35/70/M	1 mg/kg	Infection	51	58	Unknown
	10-23/69/M	1 mg/kg	Anaemia	79	Recovering	Unknown
			White blood cell count decreased	79	Recovering	Unknown
	10-26/58/M	1 mg/kg	Herpes esophagitis	68	153	Unknown
			Oral candidiasis	68	153	Unknown
			Bile duct stone	82	153	Unknown
			Biliary colic	82	153	Unknown
			Toxic skin eruption	93	Recovering	Unknown
			Psoriasis	265	Recovering	Unknown
0761-007	40-04/76/M	1 mg/kg	Rash generalized	74	Not recovered	Severe/Grade 3
	62-02/56/M	1 mg/kg	Lobar pneumonia	23	Recovered with sequelae	Life-threatening/Grade 4
0761-009			Pneumonia	8	Not recovered	Severe/Grade 3
	106-02/50/F	1 mg/kg	Pneumonia	28	Death	Death/Grade 5
	106-04/73/F	1 mg/kg	Acute myocardial infarction	8	Not recovered	Severe/Grade 3
Non-Oncology						
0761-EU-001	32/39/M	0.001 mg/kg (Single dose)	B-cell lymphoma	66	Not recovered	Severe

Note: In Study 0761-003, 3 subjects who received mLSG15 alone experienced SAEs considered possibly related to the study drugs (2 events of bacteremia and 1 event of febrile neutropenia). In addition, one subject receiving the combination of KW-0761 and mLSG15 had CMV infection considered to be possibly related to the mLSG15 but considered not related to KW-0761.

a: Age in Years at the time of the first reported event in subjects with multiple events; M=Male; F=Female

b: Event (verbatim=second malignancy) occurred 207 days after the last dose of study drug.

c: Event (verbatim=second malignancy) occurred 15 days after the last dose of study drug.

d: Not routinely collected.

mLSG15=modified LSG15 comprised of intrathecal Ara-C (Cytarabine), MTX (Methotrexate) and PSL (Prednisolone sodium succinate) in addition to the VCAP (Vincristine sulfate, Cyclophosphamide hydrate, Doxorubicin hydrochloride, Prednisolone or prednisolone sodium succinate), AMP (Doxorubicin hydrochloride, Ranimustine, Prednisolone or prednisolone sodium succinate), and VECP (Vindesine sulfate, Etoposide, Carboplatin) regimens

Source: Kyowa Hakko Kirin Pharma, Inc. Drug Safety Surveillance Database

A male subject who was enrolled as a healthy volunteer and received 0.001 mg/kg of KW-0761 in Protocol 0761-EU-001 developed B-cell lymphoma on study Day 66. Following study participation, subject presented to primary physician with swelling on the right side of his groin. It was not routine policy in this Phase 1 unit to include assessment of inguinal lymph nodes on routine physical examinations and so this was not assessed at protocol screening visit. An independent review of the case by expert hematologists/oncologists concluded that given the indolent nature of this disease and its extensive spread in this subject, it was not likely that it developed, in this timescale, as a consequence of injection of the study drug. The Investigator later concurred, noting this was subclinical disease not detected at screening.

5.7.3 Deaths

There have been 11 deaths reported while on study in subjects receiving KW-0761 all of which were considered not related to the study drug. The causes of death included bronchopneumonia, disease progression, pneumonia, and septic shock.

5.8 Concomitant Medications

During the study period, subjects should not receive treatment with systemic corticosteroids or other immunosuppressive agents including chemotherapy unless approved by the principal investigator. Topical and inhaled steroids are permitted. Treatment with antihistamines and non-steroidal anti-inflammatory drugs, including COX-2 inhibitors, are not recommended but may be continued or instituted at the discretion of the treating physician if necessary. Investigator may prescribe all other concomitant medications or treatments deemed necessary to provide adequate subject care. All prescription and nonprescription concomitant medications must be recorded in CRDB, listing generic name, indication, dose and schedule and dates of administration.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

A subject will be eligible if all of the following apply:

1. Informed Consent form signed by the subject.

2. Males and females 18 years or older at the time of dose initiation.

3. Histologically confirmed unresectable solid tumor malignancies with at least 1 measurable lesion in dose escalation. In the expansion phase, eligibility limited to metastatic triple negative breast cancer that has received prior taxane and anthracycline therapy; Metastatic NSCLC that is not ALK+ and does not have a EGFR sensitizing mutation; and metastatic gastric cancer.

4. Previously treated for advanced cancer and there are no curative therapy options available.

5. Karnofsky Performance Status ≥70 in the 30 day baseline period immediately prior to dosing.

6. All female subjects of child bearing age must be either surgically sterile, postmenopausal for at least 1 year, or using an acceptable method of contraception. Examples of adequate methods of

contraception include abstinence, intrauterine device, hormonal contraception, use of spermicide and a condom by sexual partner, or partner with a vasectomy. Adequate contraception must be used from the beginning of the screening period until at least 16 weeks after the last dose of KW-0761. Male subjects with partners of childbearing potential must use a barrier method of contraception from the day of the first dose of KW-0761 until at least 16 weeks after the last dose.

7. Evidence of adequate organ function by standard laboratory tests:
    a. Cr ≤ 1.5 X upper limit of normal (ULN).
    b. Total Bilirubin (T-Bil) ≤ 1.5 X ULN (prior diagnosis or past history consistent with Gilbert's syndrome is an exception).
    c. AST and ALT ≤ 2.5 X ULN.
    d. Plts ≥ 100,000 /μL
    e. Hgb ≥ 9.0 g/dL.
    f. Absolute neutrophil count (ANC) ≥ 1000/mm^3

8. Life expectancy > 12 weeks

9. Previously treated for advanced cancer with no additional therapy options available known to prolong survival.

6.3 Subject Exclusion Criteria

A subject will be ineligible if any of the following apply:

1. Evidence of clinically significant central nervous system (CNS) metastases or symptomatic CNS metastases within 30 days prior to dosing.

2. History of autoimmune disease, except for vitiligo, diabetes, and autoimmune thyroiditis.

3. A history of any major surgery within 6 weeks prior to dosing.

4. Any history of systemic anti-cancer therapy (standard or experimental) completed within 30 days prior to dosing, with the exception of palliative ablation of lesion(s) as long as measurable disease lesion(s) remain for evaluation of exploratory endpoints.

5. Any concomitant serious physical illness other than cancer (i.e., immune deficiency disease, bleeding disorder, etc.) within 1 year prior to dosing.

6. Any history of Stevens-Johnson syndrome.

7. Clinically significant heart disease, defined as NYHA Class III or IV.

8. Any allergic reaction to a previously administered monoclonal antibody or other therapeutic protein.

9. Any significant systemic infection within 4 weeks prior to dosing.

10. Pregnancy or breast-feeding.

11. An existing diagnosis of HIV, hepatitis B, hepatitis C, or any current laboratory findings or clinical signs and symptoms that suggest these conditions.

12. Subjects with active herpes simplex or herpes zoster. Subjects with a history of herpes zoster who have had an outbreak within the last year will also be excluded. Subjects on prophylaxis for herpes who started taking medication at least 30 days prior to study entry, should continue to take the prescribed medication for the duration of the study.

13. Unresolved immune-related adverse events following prior biological therapy

14. Use of any investigational drugs within 30 days prior to dosing.

15. Any condition that requires or is likely to require treatment with systemic corticosteroids within the Core Study Period and short term follow-up.

16. Subjects that have had a myocardial infarction within the last 6 months.

17. Subjects on any immunomodulatory drug.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Before being enrolled, subjects must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. An informed consent form will be prepared and given to the subject. This document will contain all the elements required by FDA CFR Part 50 the ICH E6 Guideline for GCP and any additional elements required by local regulations. The document must be in a language understandable to the subject. Where required by local law, the person who informs the subject must be a physician.

After reading the informed consent form and any other IRB approved subject-specific study information, and having had ample opportunity for his questions to be answered by an adequately trained medical professional, the subject must give consent in writing before any study-specific procedures can commence. The subject's consent must be confirmed at the time of consent by the personally dated and timed signature of the subject.

A copy of the consent document and any other subject-specific information reviewed as part of the consent process must be given to the subject The original signed consent document will be retained by the Investigator.

If the subject is unable to read, oral presentation and explanation of the patient information sheet and the informed consent form and any information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated and timed signature of the subject or by a local legally recognized alternative (e.g., the subject's thumbprint or mark). The witness to the informed consent discussions must also sign and personally date the consent document.

The Investigator will not undertake any measures required for the clinical study until valid consent has been obtained.

This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients referred for treatment without exclusion as to age, gender, or ethnic background. Pregnant women are excluded from participation in this study.

This cost of this study will be covered by a combination of funds from Kyowa Hakko Kirin Pharma, grants awarded to the Co-Principal Investigator, and additional funding from the Ludwig Institute for Cancer Research at MSKCC.

The anticipated study accrual time is 2.5 years.

8.1 PRETREATMENT EVALUATION

Pre-treatment evaluations used to determine the subject's study eligibility must be completed within 30 days prior to the first dose of KW-0761, except as otherwise specifically noted below. Written informed consent must be obtained prior to any study-specific screening evaluations and before subject enrollment.

All subjects must undergo the following screening evaluations:

- medical history including cancer history and prior therapies, as well as concomitant medical conditions and medication use
- physical examination (including height [at baseline only] and weight measurements)
- Karnofsky performance status
- vital signs
- ECG
- urine pregnancy test in women of childbearing potential
- urinalysis
- chemistry profile
- hematology profile
- coagulation profile
- flow cytometry of lymphocyte subsets
- serum cytokines
- CMV Ag and Ab
- quantitative immunoglobulins
- HIV
- hepatitis panel
- concomitant medication assessment and those medications taken 30 days prior to the first dose of study medication
- chest, abdominal, pelvic CT or MRI scans or PET/CT (within 30 days prior to the first dose of KW-0761)

Results of all screening evaluations must be reviewed by the Principal Investigator or his/her designee to ensure that all eligibility criteria have been satisfied prior to subject treatment.

9.1 TREATMENT/INTERVENTION PLAN

9.2 Dose Schedule

As shown in Section 4.1, in the first treatment course, KW-0761 will be administered i.v. once a week for four weeks (Cycle 1) and subsequently every 2 weeks for 4 weeks (Cycle 2). Subsequent treatment courses are permissible for subjects demonstrating a response or maintaining stable disease and will consist of an infusion of KW-0761 every other week. Each subsequent course (treatment course 2, treatment course 3, etc.) will be defined as completion of two additional infusions of KW-0761 over 4 weeks. In the absence of progression or toxicity subjects may continue treatment up to 1 year. If a subject experiences an overall CR, the subject may continue on study for up to an additional four infusions beyond CR, then discontinue treatment in order to determine duration of response. If a subject experiences a PR or SD, the subject may continue therapy after consultation between the

Investigator and the Principal Investigator until disease progression occurs or other withdrawal criteria are met (refer to Section 4.8, Criteria for Study Termination).

Standard 3+3 cohorts for safety and DLT detection will be utilized (Table 1). Each cohort will consist of at least three subjects. If DLT is observed in 0/3 subjects, escalation to the next dose level will occur. If DLT detected in 1 of 3 subjects, then three more subjects will be added at that dose level. If DLT is demonstrated in an additional subject, dose escalation will cease (see Section 14 - Biostats for a summary).

Phase II of the study will enroll a total of 48 subjects, 16 patients in 3 tumor-specific expansion cohorts each treated with the MTD (or highest dose tested) as determined in Part 1 of the study. The 3 tumor-specific expansion cohorts will include non-small cell lung cancer, gastric adenocarcinoma, and triple-negative (negative for immunohistochemical expression of the estrogen receptor, progesterone receptor, and the Her2 protein) breast adenocarcinoma.

9.3 Toxicity Definitions

All AEs will be evaluated and reported according to the NCI CTCAE v.4.03. For toxicity grading based on laboratory tests, an abnormality must be confirmed (when appropriate) by repeat testing.

9.3.1 Dose Limiting Toxicity

The occurrence of the following toxicities will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

The definition of DLT is any ≥ Grade 3 hematologic or non-hematologic toxicity that is related to treatment.

Exceptions:

The following are exceptions to the definition and will be considered a DLT if:

- Grade 4 neutropenia > 7 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding

In the case of Grade 2 immune related adverse events (irAE, defined below) study drug administration will be delayed until event diminishes to Grade 1 or less.

Immune related Adverse Events

An irAE is defined as a clinically significant adverse event of any organ that is associated with study drug exposure, of unknown etiology, and is consistent with an immune-mediated mechanism. Serologic, immunologic, and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Given the intended mechanism of action of KW-0761, particular attention will be given to adverse events that may follow enhanced T-cell activation such as dermatitis and colitis, endocrinopathies, or other irAEs.

9.3.2 Infusion Reactions: Grading and Management

Intravenous administration of biologic agents carries a potential risk of hypersensitivity reactions. Infusion reactions will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Table 5 outlines the infusion reaction grading system, associated symptoms, and the recommended actions to be taken regarding treatment. Reactions occurring within 24 hours after the start of KW-0761 infusion will be considered to be infusion related AEs. Premedication with acetaminophen 650 mg orally and diphenhydramine 50 mg i.v. or other antihistamine will be administered to all subjects.

As with all AEs, infusion-related signs or symptoms which, in the Investigator's judgment, are not related to hypersensitivity reactions (e.g., dyspepsia, urinary frequency, etc.) should be recorded and graded as AEs according to NCI CTCAE v.4.03 criteria in CRDB. Based on nonclinical in vitro and in vivo data, KW-0761 administration is not expected to cause cytokine release syndrome (CRS). Although there is significant overlap in the clinical presentations of anaphylaxis and CRS and either can occur during or within 2 hours of completion of infusion of biologic agents, some symptoms, such as arthralgia and chills, are more likely to be due to CRS than anaphylaxis. The NCI CTCAE v.4.03 will be used to grade and report infusion reactions consistent with CRS.

Stopping Rules will not apply to a specific toxicity if it is clearly unrelated to KW-0761 infusion (e.g., laceration, burn, or similar accidental trauma unrelated to some other infusion-related AE).

Table 5: Infusion Reaction Grading

Grade	Symptoms	Course of Action
1	Transient flushing or rash, drug fever (≥38˚C)	No intervention required
2	Rash, flushing, urticarial, dyspnea, drug fever (≥38˚C)	Decrease the infusion rate by 50% and proceed with dosing.
3	Symptomatic bronchospasm and urticarial with need for parenteral medication(s), allergy-related edema/angioedema, hypotension	Stop infusion. Give supplemental oxygen and bronchodilators as necessary. Subject will not receive any further KW-071.
4	Anaphylaxis	Stop infusion. Administer no further KW-0761 to subject. Contact principal investigator immediately. Investigator(s) review within 72 hours. Further actions related to study conduct will be submitted to IRB for approval before initiation.
5	Death	Contact principal investigator immediately. Further cohort dosing suspended. Investigator(s) review within 72 hours. Further actions will be submitted to IRB for approval before study resumed.

9.3.3 Treatment of Emergent Skin Rash

In the event a patient develops a treatment emergent skin rash, the following measures must be taken to appropriately document the event:

Initial Work-up of all skin rashes (new and re-challenge)

1) Photograph the rash.
2) If the rash is ≥ Grade 2 or if the affected area cannot be differentiated from a new area of cutaneous metastasis, a biopsy must be performed. Biopsy the rash as well as an area of unaffected skin in order to compare possible drug eruption to background involved skin.
3) Confer with Principal Investigator after completion of one week of treatment with topical corticosteroids to assess response to treatment.
4) Forward all results to the Principal Investigator and discuss a treatment plan with medical follow up.
5) Biopsy should be read by the dermatopathologist at the study center.

Rash Treatment Guidelines (after initial work-up):

Grade 1 rash (drug related or non-drug related)

1) Treatment with study drug may continue.
2) Treat rash with topical corticosteroids as needed.

Grade 2 or above rash (drug related)

1) Treatment with study drug must be stopped.
2) Treat rash with 2-week course of topical corticosteroids.
3) After 2-week course, re-assess rash per the steps outlined in initial assessment; if resolved completely or to Grade 1, study drug treatment may be resumed. If not resolved, contact the Principal Investigator for further discussion.
4) Subjects with Grade 3 or 4 rash will not receive any further KW-0761.

Grade 2 or above rash on re-challenge

1) If rash recurs and becomes a Grade 3, the patient must be discontinued from the trial and the rash work up above must be completed.
2) If the rash recurs at a Grade 2, follow the steps above for Grade 2 Rash.
3) If the rash recurs at Grade 2 or higher for a third time, the rash work up must be performed and the patient must be discontinued from the trial.
4) Subjects with Grade 3 or 4 rash will not receive any further KW-0761.

9.3 Assessment of Safety

Safety is a primary endpoint for this study. Safety will be evaluated for all treated subjects using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, and clinical laboratory tests. The incidence of observed adverse events will be tabulated and reviewed for potential significance and clinical importance. The reporting period for safety data will be from the time following the subject's written consent to participate in the study until 90 days after the last dose. The timing of all Safety assessments, including AE reporting and laboratory assessments, is shown in the Schedule of Assessments, Table 2.

9.4 Serious and Serious Adverse Events

9.4.1 Definition of Adverse Events

An AE is any untoward medical event that occurs in a subject who has received an investigational product, and does not necessarily need to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the product.

All AEs will be evaluated and reported according to the NCI CTCAE v.4.03.

9.4.2 Treatment Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is an AE that begins or that worsens in severity after the start of the first exposure to KW-0761. Only TEAEs will be recorded in CRDB. For the purposes of this study, the terms "AE" and "TEAE" may be used interchangeably. Adverse events that occur during the Screening and Baseline periods are not treatment emergent and will be recorded in the subject's medical records, but not in CRDB.

An illness present at study entry is considered a pre-existing condition, not an AE. Pre-existing conditions will be recorded in CRDB. If a subject experiences clinically relevant worsening of a pre-existing condition after any KW-0761 has been administered, this will be considered an AE.

Signs and symptoms present at baseline will be documented as pre-existing symptoms in CRDB.

9.4.3 Serious Adverse Event

An SAE is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening,[A]
3. Requires in-patient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly or birth defect, and/or
6. Is another medically important condition[B]

A. The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have

caused death if it were more severe. The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to the subject's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

B. Medically important conditions that may not result in death, but may be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Reporting requirements for SAEs are described in Section 9.4.

9.4.4 Relationship to KW-0761

The relationship of all AEs to KW-0761 will be determined by the Investigator on the basis of clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents", NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is clearly related to the investigational agent)

Probably related (The AE is likely related to the investigational agent)

Possibly related (The AE may be related to the investigational agent)

Unlikely related (The AE is doubtfully related to the investigational agent)

Unrelated (The AE is clearly not related to the investigational agent)

N.B.: When making the assessment of causality, it should be taken into consideration that immunomodulatory agents have the potential to cause late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in this protocol may support these evaluations.

9.5 Safety Criteria for Advancement, Adjustment, or Stopping Dosing Within a Cohort

This is safety and tolerability study. Safety monitoring will be conducted by the Principal Investigator. Subjects will be monitored at the investigative site according to the schedule of assessments outlined in Table 2. Additional assessments to evaluate and/or treat any AEs may be performed at the discretion of the Principal Investigator. In the event that a subject will need to undergo palliative surgery or radiation, the schedule of dosing and assessments will be modified to allow for the treatment to be administered. The adjustments will be made in coordination with the Principal Investigator and the subject’s physicians.

9.5.1 Dose Limiting Toxicity

Patients in each cohort must complete the first 4 weeks of study therapy prior to enrollment of subsequent cohorts. For the purpose of determining the MTD, the timeframe for evaluating patients for DLT will be within 4 weeks of study therapy. All adverse reactions should be considered relevant to determining dose limiting toxicity and to reporting, unless the event can clearly be determined to be unrelated to the drug. Sites must notify the Principal Investigator within 24 hours of having knowledge of DLT. All investigators in the study will be notified of any DLTs at each dose level before dose escalation.

Subjects experiencing a DLT during any course of treatment should receive no further administration of KW-0761. However, subjects exhibiting clinical benefit and who experience DLT may be eligible for further administration of KW-0761 on a case by case basis following discussion with the Principal Investigator.

A dose limiting toxicity (DLT) will be defined as any toxicity that does not have a clear-cut alternative explanation. Any of the following, specified below, will be considered a DLT:

- >Grade 3 non-hematologic toxicity
- >Grade 3 hematologic toxicity
- >Grade 3 allergic reaction/hypersensitivity reaction (including drug fever)
- >Grade 3 cytokine release syndrome/acute infusion reaction

9.5.2 Exceptions to Dose Limiting Toxicity

The following are exceptions to the definition and will be considered a DLT if:

- Grade 4 neutropenia > 7 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with clinically significant bleeding

Patients who enter the trial with Grade 2 elevation of liver enzymes due to hepatic involvement by malignancy must have an increase in hepatic enzymes to Grade 3 that persists for at least 7 days for this toxicity to represent a DLT.

9.5.3 Definition of Maximum Tolerated Dose (MTD) and definition of Maximal Dose Level

The MTD is defined as the dose below that dose at which at least 2 of up to 6 subjects in a dosing cohort experience DLT. The MTD will be determined during Phase 1. In the absence of MTD, the maximal dose level is the highest dose evaluated in this study without evidence of DLT.

9.6 Dose Escalation

Toxicity data for each cohort will be reviewed prior to dose escalation. The dose for the first cohort will be 0.5 mg/kg. In the absence of a DLT, dose will be escalated as indicated in the cohorts listed in Table 1. Dose escalation will cease when at least one of the following endpoints is reached:

- The MTD is exceeded; Or
- A cohort of at least 3 subjects has been dosed with 10 mg/kg KW-0761

Dose escalation will be based on at least three evaluable subjects receiving four complete infusions of KW-0761.

9.7 Cohort Size and Stopping Rules

See Table 6 for a summary.

Table 6. Determination of DLT and MTD

Number of Subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter up to three more subjects at this dose level. If 0 of these 3 subjects experience DLT, proceed to the next dose level. If 1 or more of this group develop DLT, then dose escalation is stopped, and the next lower dose level is declared the MTD. Three additional subjects will be entered at the next lower dose level if only 3 subjects were previously treated at that dose.
≥2	Dose escalation will be stopped. The next lower dose level is declared the MTD. Three additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.

9.8 Replacement of Subjects

During the dose escalation phase of this study subjects who do not complete the first four infusions for reasons other than a DLT will be replaced.

9.9 Phase II – Preliminary Assessment of Efficacy and Further Assessment of Safety

After determination of the MTD or maximal dose level if MTD is not exceeded, additional subjects will then be enrolled and treated at that dose if feasible, or a lower dose if not feasible in three disease specific cohorts. Fourty-eight subjects, are to be treated with the dose determined from the initial portion of the study.

If during Phase I/II portion of the study compelling evidence collects of response in a particular tumor type the protocol may be amended to include an expansion cohort.

There will be no dose reductions allowed during the Phase II portion of the study.

9.11 Pharmacodynamic Assessments

Pharmacodynamic assessments will be performed on all patients in this study. Available research blood and tumor samples will be delivered to the Immune Monitoring Facility (IMF) for processing and cryopreservation. Available stool samples will be similarly brought to the Molecular Microbiology Core Facility. Subjects will bring in samples when feasible. It is understood that the bowel habits of subjects will vary widely and as such it is likely that not all collections are possible, if this is the case subjects will be allowed to continue on study.

If a site of tumor is readily available as a cutaneous lesion a simple punch or excisional biopsy under local anesthesia can be performed by the co-principal investigator or qualified personnel. If tumor is as readily accessible then an image-guided core needle biopsy will be obtained following consultation with the radiology staff to determine the overall risk of the procedure. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. If a surgical procedure is performed for a clinical indication a sample may be used for research purposes. During the course of treatment a decision may be made to perform the post-treatment biopsy earlier than 15 days if there is evidence to suggest a possibility that by day 15 there will be no available tumor for biopsy due to a rapid clinical response. Similarly the biopsy may be performed later than 15 days if there is evidence to suggest a delayed response.

Tumor tissue obtained from biopsies will be divided equally for fresh frozen paraffin embedding and cryopreservation by the IMF.

9.11.1 $CCR4^+$ T cell depletion

The degree of depletion of $CCR4^+$ T cells by KW-0761 will be determined by flow cytometry. The proportion of $CCR4^+$ T cells to other T cell subsets as well as the concentration in a fixed volume of blood will expressed in relation to base line levels as well as time.

9.11.2 Serum Biomarkers

Pre-treatment and on-treatment serum levels of chemokines, cytokines, and tumor-associated soluble proteins will be assessed by techniques that may include but are not limited to, ELISA or multiplex assays. Analytes may include markers of inflammation, immune activation, host tumor growth factors, and tumor-derived proteins. These assays will take place in the Immune Monitoring Facility (IMF) and a messenger will bring the samples to the IMF from the ITC. The sample will need to arrive to the ITC within 6 hours of blood draw.

Serologic assays using multiplexed ELISA to determine antibody titers to tumor-associated antigens will also be performed by the IMF. Theses assays are used to estimate the titer of antibodies specific to one or more tumor-associated antigens, including but not limited to cancer-testis (CT) antigens such as NY-ESO-1, in human serum or plasma samples. Monitoring of potential changes in particular tumor antigen-specific antibody responses during the course of cancer immunotherapy may predict response or provide further understanding of the mechanism of action of KW-0761.

9.11.3 Immunophenotyping

Immunophenotyping will be determined using flow cytometry to determine the effect on individual lymphocyte subsets in peripheral blood mononuclear cells (PBMC) and in tumor if sufficient tumor

tissue is present. 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, CD45RA, CD45RO, LAG3, GARP, PD1, and CTLA4. Activation markers such as CD44 and CD69, will also be examined. These assays will take place in the Immune Monitoring Facility (IMF).

In order to determine if the depletion of Treg cells has an effect on pre-existing immunity to multiple non-tumor antigens, PBMC will be analyzed with a panel of HLA tetramers to common antigens including those used in routine vaccinations. This will be done in collaboration with Dr. Ton Schumacher of the Netherlands Cancer Institute who has developed and validated the panel of HLA-Tetramers. In order to choose tetramers that are specific to the individual patients HLA, a sample of PBMCs will undergo HLA typing by the New York Blood Center. The samples that will be sent to The New York Blood Center as well as to Dr. Schumacher's group will be de-identified to ensure that privacy will be maintained.

Phenotypic analysis of TILs by immunohistochemistry will be performed to identify and characterize tumor infiltrating immune cells. We will also assess tumor cell apoptosis, hypoxia, vascularization, and proliferative activity as described. These assays will be performed by MSKCC tumor pathology core, where tumor hypoxia, apoptosis, and proliferation indices are analyzed in a standardized manner by MSKCC Molecular Cytology facility. The tumor tissue will be accessioned and stored by the IMF until analysis.

Archival tumor biopsy material if present may be examined for biomarkers of interest and/or infiltrating immune cells and their presence or absence correlated with observed clinical outcomes. If such an analysis is planned a separate tissue procurement protocol will be submitted for review.

9.11.4 Cellular Assays

To explore if KW-0761 has an effect on the function of T cells assays that determine the production of effector molecules including but not limited to IFN-g and Granzyme B will be assessed by flow cytometry in response to non-specific or antigen specific restimulation. Examples of antigen specific stimulation include the use of either tumor specific antigens or commonly exposed antigens such as influenza proteins. These assays will be performed on cryopreserved PBMC in the IMF.

The IMF may also perform ELISPOT, flow tetramer staining, and/or intracellular polyfunctional cytokine staining, TCR Vβ Repertoire analysis and Spectratyping to further characterize tumor-antigen specific $CD4^+$ and $CD8^+$ T cell response before and after treatment. PBMCs and TILs from relevant tissue will be archived for all patients to support complete analysis of the profile.

9.11.5 Gene Expression Profiling

Analysis of the transcriptome of PBMC or tumor tissue may provide further understanding of the mechanism of action of KW-0761. Cryopreserved PBMC and tumor tissue will submitted to the Integrated Genomics Core Facility for RNA extraction, SMARTer amplification, and mRNA sequencing on the HiSeq sequencing platform. Analysis of the data will be performed with the assistance of the bioinformatics core facility. Further analysis of gene expression may be performed with quantitative real-time polymerase chain reaction (qPCR) or additional multiplexed gene expression assays to detect expression of selected immune-related genes.

9.11.6 Stool Microbial Composition and Metabolite Analysis

The composition of the stool microbiota modulates the activity of the immune system through the production of various bioactive metabolites. Modulation of the immune system by KW-0761 may alter the composition of the stool microbiota that can lead to adverse events such as colitis. Thus, we will collect fecal samples from patients prior to, and after treatment and assess changes in composition of microbial community using 16S RNA sequencing and metagenomic analysis as a correlate for intestinal inflammation as a result of Treg cell depletion. Analysis of various bacterial metabolites including but not limited to short-chained fatty acids will also be performed by nuclear magnetic resonance or chromatography. Subjects at home will collect the stool samples with the use of a stool collection kit. The kit will include detailed instructions on collection, handling, and transport of the sample. When the sample is brought to the ITC, it will be refrigerated and sent to the Molecular Microbiology Core Facility by a messenger. The sample should arrive at the core facility within 12 hours of arrival at the ITC. The sample should be collected by the patient within 24 hours of arrival to the ITC.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Treatment course Evaluations

A series of clinical tests and procedures will be performed at different intervals throughout the study (Table 2).

Evaluations to be performed periodically during the study include:

- Physical examination
- Karnofsky PS
- Vital signs
- ECG
- Urinalysis
- Chemistry profile
- Hematology profile
- Coagulation profile
- Flow cytometry of peripheral blood lymphocytes
- AE assessment
- Concomitant medication assessment
- Cross-sectional imaging (Chest, abdominal, pelvic CT or MRI scans, or PET/CT)
- Assessment of tumor response (AJCC, TNM and irRC)

10.2 Disease Monitoring Criteria

Disease stage will be assessed by the AJCC TNM Clinical Staging [107]. Clinical stage from medical history will be documented from medical records during Screening (Inclusion/Exclusion Review). Clinical staging will be assessed by review of medical records, review of pathologic staging of the most recent lymph node biopsies, and imaging for evaluation of metastases within 30 days of KW-0761

dosing and at Day 15 of Cycle 2. Clinical staging will be documented at Baseline/Screening and repeated and documented at Day 15 of Cycle 2. When possible, tumor progression will be assessed according to irRC at Baseline, Day 15 of Cycle 2 and every 2 cycles thereafter, and as data are available and/or clinically indicated- during Long-term Follow-up [108,109].

The irRC criteria allow for continued treatment beyond progression of disease (in order to confirm response). Treatment beyond what would be considered progression of disease using RECIST 1.1 criteria will be permitted if the following criteria are met:

- Investigator-assessed clinical benefit, and do not have rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g. CNS metastases)

10.3 Discontinuation of Study Therapy

In accordance with the Declaration of Helsinki, ICH Good clinical Practice Guidelines, and the US FDA Regulations, a research subject has the right to withdraw at any time for any reason without prejudice to future medical care. Further criteria for removal from the study are described in Section 13. In the absence of a medical contraindication or significant protocol violation, every effort will be made by the Principal Investigator to keep the subject in the study; however, should the subject decide to discontinue treatment, all efforts will be made to complete and report the observations as thoroughly as possible, including a complete final evaluation at the time of the subject's withdrawal with an explanation of why the subject is withdrawing from the study. If the subject is agreeable they will be eligible for short term and long term follow up at listed in Table 2 regardless of duration of treatment. If the subject declines consent for final assessments these will not be done and a note will be recorded in CRDB.

10.4 4 Post-therapy Monitoring

The Investigator can elect to conduct additional tests and/or follow-up visits in clinic during the post-therapy monitoring period as needed to evaluate and/or treat any adverse event (AEs).

Subjects will return for assessments at weeks 2, 3, 6, 12, 18, 24 following the last dose (Figure 6). Telephonic assessments or medical record reviews will occur at Months 6, 12, 18, and 24 after last dose is administered. The Investigator can elect to conduct additional tests and/or follow-up visits in clinic during this period as needed to evaluate and/or treat any adverse event (AEs).

10.4.1 Short-Term Follow-Up (STFU)

Following the end of treatment or treatment completion date, a 24-week short term follow-up (STFU) period of observation will begin. Patients will be seen at weeks 2,3,6,12,18, and 24 following the last dose during which the following evaluations will take place (see Table 2):

- Karnofsky Performance Status (every visit)
- Physical Examination (every visit)
- Vital Signs (every visit)
- CBC (weeks 12, 24)
- Stool analysis (Weeks 3, 12, 24)
- Flow Cytometry and Serum Cytokines (Weeks 3, 12, 18, 24)
- Tumor Imaging (Week 18)

10.4.2 Long-Term Follow-Up (LTFU)

Telephone assessments or medical record reviews will occur at 6, 12, 18, and 24 months after the end of the Short-term follow up period (Table 2), the end of treatment date or treatment completion date. Vital status and any new therapies started will be determined.

11.0 TOXICITIES/SIDE EFFECTS

As with all therapeutic proteins, there is a potential for immunogenicity. Subjects will be monitored for autoimmune syndrome development, including but not limited to colitis, dermatitis, thyroiditis and uveitis. Subjects administered KW-0761 may be at risk of developing an infection, as KW-0761 may affect host defenses. The impact of treatment with KW-0761 on the development and course of active and/or chronic infections is not fully understood, therefore, subjects developing an infection during treatment with KW-0761 should be monitored closely. Subjects should be monitored for tumor lysis syndrome, a metabolic oncologic emergency associated with hematologic malignancies that presents as severe electrolyte abnormalities. Signs and symptoms include azotemia, acidosis, hyperphosphatemia, hyperkalemia, hypocalcemia, and acute renal failure. Treatment of tumor lysis syndrome includes in-subject monitoring, vigorous fluid resuscitation, and allopurinol or urate oxidase therapy to lower uric acid levels, urinary alkalinization, and hemodialysis.

Subjects experiencing Grade 4 neutropenia should have a white blood cell count done every other day until absolute neutrophil count (ANC) is above 1,000 cells/µl. If the Grade 4 neutropenia persists for > 7 days, this is a DLT and subject must be removed from study. Administration of G-CSF and/or other appropriate supportive care measures should be considered.

Additional information about potential toxicities can be found in section 9.2.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Disease Progression Monitoring Criteria

Disease stage will be assessed by the AJCC TNM Clinical Staging [107]. Clinical stage from medical history will be documented from medical records during Screening (Inclusion/Exclusion Review).

Clinical staging will be assessed by review of medical records, review of pathologic staging of the most recent lymph node biopsies, and imaging for evaluation of metastases within 30 days of KW-0761 dosing at Week 8, and every eight weeks thereafter. Clinical staging will be documented at Baseline/Screening and repeated and documented at Day 15 of Cycle 2, and every 2 cycles thereafter. When possible, tumor progression will be assessed according to irRC at Baseline, at Day 15 of Cycle 2, and every 2 cycles thereafter, and as data are available and/or clinically indicated- during Long-term Follow-up [108,109]. See Appendix I for detailed monitoring criteria.

If possible a tumor biopsy will be obtained at Baseline and at Day 15 (+/- 4 days) from all subjects. Qualified personnel trained in the procedure will take the tumor biopsy. If a site of tumor is readily available as a cutaneous lesion a simple punch or excisional biopsy under local anesthesia can be performed by the principal investigatory or qualified personnel. If tumor is not readily accessible then an image-guided core needle biopsy will be obtained following consultation with the radiology staff to determine the overall risk of the procedure. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. If a surgical procedure is performed for a clinical indication a sample may be used for research purposes. During the course of treatment a decision may be made to perform the post-treatment biopsy earlier than 15 days if there is evidence to suggest a possibility that by day 15 there will be no available tumor for biopsy due to a rapid clinical response. Similarly tumor biopsy may be delayed if there is evidence of a delayed response.

From the biopsy specimens, immune cell subsets including dendritic cells, T and B lymphocytes will be evaluated by IHC and flow cytometry for morphology, activation, and maturation status. Isolation of individual populations of lymphocytes or tumor cells may be performed for gene expression analysis and DNA/RNA sequencing. Additional correlative exploratory immunologic studies including, but not limited to, enumerating and characterizing circulating cytokines, immune cells, and tumor cells will be performed.

13.1 CRITERIA FOR REMOVAL FROM STUDY

In accordance with the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and the US FDA Regulations, a research subject has the right to withdraw at any time for any reason without prejudice to future medical care. The investigators also have the right to withdraw subjects. Should a subject (or legally authorized representative) decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible.

A complete final evaluation should be made at the time of withdrawal with an explanation of why the subject is withdrawing. An attempt should be made to perform a follow-up study visit at the time of withdrawal. This discussion will be documented in the EMR.

Subjects may be removed from study if one or more of the following occur:

- Significant protocol violation by the Investigator.
- Significant subject noncompliance.
- Refusal of the subject to continue treatment or observations.
- Disease recurrence or progression that prevents further participation.
- Investigator decides that termination is in the subject's best medical interest.
- Lost to follow-up.

With the consent of the subject or the legally authorized representative the Investigator may determine that limited data collection may be continued (e.g., through medical record review) for the duration of the study after a subject has withdrawn.

Subjects who do not complete the study for reasons other than dose limiting toxicity (DLT) will be replaced at the discretion of the Principal Investigator. In an effort to have a sufficient number of patients to evaluate saphety in the Phase I portion of the trial and to obtain 16 evaluable patients per tumor specific cohort in the Phase II portions replacement of such patients will also occur. Inevaluable patients will be reported. All subjects will be included in the analysis of results.

14.1 BIOSTATISTICS

Categorical variables will be summarized using counts and percentages, while continuous variables will be summarized using the mean, median, standard deviation, minimum, maximum, and number of observations. All summaries will be presented by cohort. Any statistical testing performed will be two-tailed at the 5% significance level. A detailed description of statistical analyses will be presented in a Statistical Analysis Plan, which will be completed and approved by the PI before the database is locked.

This phase I/II trial to determine the maximum tolerated dose (MTD) of mogamulizumab (KW-0761) in patients with advanced and/or metastatic solid tumors. A standard 3+3 design will be utilized to determine the MTD. Four dose levels of KW-0761 will be investigated (0.5mg/kg, 1mg/kg, 3mg/kg, 10mg/kg). Patients will be treated in cohorts of size three to six and the dosage will be escalated if the clinical toxicity is acceptable. Toxicity severity will be graded according to the CTCAE (ver. 4.03).

A dose-limiting toxicity (DLT) will be defined as any toxicity that does not have a clear-cut alternative explanation. Any of the following, specified below, will be considered a DLT:

≥ Grade 3 non-hematologic toxicity
≥ Grade 3 hematologic toxicity
≥ Grade 3 allergic reaction/hypersensitivity reaction (including drug fever)
≥ Grade 3 cytokine release syndrome/acute infusion reaction

The following are exceptions to Dose-Limiting Toxicity
For neutropenia and thrombocytopenia, the following criteria must be met to be considered a DLT:

Grade 4 neutropenia lasting >7 days
Grade 4 thrombocytopenia
Grade 3 thrombocytopenia with bleeding

Patients who enter the trial with Grade 2 elevation of liver enzymes due to hepatic involvement by malignancy must have an increase in hepatic enzymes to Grade 3 that persists for at least 7 days for this toxicity to represent a DLT.

The design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, and increase the chance of escalating the dose when the probability of DLT is low. The maximum tolerated dose (MTD) is defined as the highest dose level where a DLT occurs within at most one out of six patients treated. The escalation scheme is as follows:

(1) If none of the initial three patients in a cohort experiences a DLT, then a new cohort of three patients will be treated at the next higher dose level.

(2) If one of the three patients in a cohort experiences a DLT, then up to three additional patients will be treated at the same dose. Escalation will continue if only one of the six patients experiences DLT.

(3) If two or more patients in a cohort experience DLT, then the MTD will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered the MTD.

(4) If only three patients were treated at a dose level under consideration as the MTD, then up to three additional patients will be accrued. If no more than one of the six patients at that dose level experience a DLT, then that dose level will be confirmed as the MTD. If two or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion.

The MTD is defined as the highest dose studied for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the NCI Common Toxicity Criteria.

Table 7 below gives the probabilities of dose escalation based on true DLT risk in the 3+3 design.

	True DLT rate								
Probability of escalation	10%	20%	30%	40%	50%	60%	70%	80%	90%
	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

Phase II portion: Additional patients will be accrued to the disease specific expansion cohorts at the MTD for evaluation of safety, tolerability, pharmacodynamics, and activity potential in the Phase II portion. The diseases included in these cohorts include triple-negative breast carcinoma, non-small cell lung carcinoma, and gastric adenocarcinoma for which there will be cohort sizes of 16 subjects for a total of 48 subjects in the Phase II portion. The primary activity parameter is disease response, as measured by irRC at 6 months from the initiation of therapy in the phase II portion of the expansion cohorts. It is assumed that none of the subjects would have a response if they had not received any therapy and the response rate (RR) for subjects treated with KW-0761 would be 10%. A one-sample exact binomial test will be used in testing the alternative hypothesis H_a: $RR_{\text{with treatment}}$ = 10% against the null hypothesis H_0: $RR_{\text{without treatment}}$ = 0.1%. A sample size of 16 evaluable subjects is required to provide more than 80% power in a one-sample exact Binomial test at the significance level of 0.05. If one response is observed out of 16 patients in a particular cohort then the treatment will be considered worthy of further study in that cohort.

The 10% response rate was chosen based on the response rates observed with ipilimumab, arguably the most successful and best-studied immunotherapy in current clinical use, whose mechanism of action is mediated at least in part through Treg cell depletion [110]. The Phase II study of ipilimumab showed a best overall response rate of 11.1% in heavily pretreated melanoma patients [111]. The best overall response rate of 10.9% in the Phase III clinical trial of ipilimumab in patients with metastatic melanoma which translated to an improved overall survival [34].

Overall and progression-free survival will be estimated using Kaplan-Meier methodology. Toxicity will be reported by type, frequency and severity according to the most recent NCI Common Toxicity Criteria

Response rate (CR+PR) and disease control rate (CR+PR+SD) (estimated by RECIST and immune related response criteria) will be calculated along with the corresponding confidence interval will be reported. Duration of response will be summarized among responders.

A minimum of of 2 patients and a maximum of 24 patients will be accrued to the phase I portion of this trial. Forty-eight patients will be accrued to the phase II portion of the trial. It is anticipated that 8 patients per month will be accrued and the entire study will be completed within 4 years.

For the correlative studies, the analysis is primarily exploratory for the subjects from whom we obtain biologic samples. Appropriate descriptive statistical measures will be used to summarize the data. For each tumor specific cohort separately, pre and post comparisons will be assessed on the biopsy specimens. For binary markers, McNemars test and for continuous markers, the Wilcoxon signed rank test will be utilized to assess changes pre versus post treatment.

14.2 1 Pharmacodynamic Analysis

Correlative studies will be performed on biologic specimens obtained from subjects in the Phase I and Phase II portions of this trial.

Flow cytometric results for lymphocyte subsets and CCR4+ T cell counts will be tabulated and presented graphically by cohort and time. The results of other PD assessments (will be summarized using descriptive statistics.

Treg cells constitute a significant proportion of TILs and based on their potent immunoregulatory properties we hypothesize that Treg cell depletion will lead to significant alteration in the tumor immune microenvironment. A tumor biopsy will be obtained at Baseline and at Day 15 and investigated for the extent and consequences of Treg depletion. The tumor biopsy will be taken by qualified personnel trained in the procedure. In these specimens, immune cells and cell subsets including dendritic cells, and T and B lymphocytes as well as their subsets will be qualitatively and quantitatively evaluated by IHC for morphology, activation, and maturation status. Phenotypic analysis of TILs by flow cytometry will be performed using validated antibody panels to identify and characterize tumor infiltrating T cells and myeloid cells. Activation state of CD4 and CD8 T cells will be determined by staining for lineage specific transcription factors (T-BET, GATA3, FOXP3, RORC) as well as intracellular cytokine analysis following in vitro re-stimulation. Correlative exploratory immunologic studies including, but not limited to, circulating cytokines, circulating immune cells, and tumor cells will be performed.

Treg cells are critical mediators of peripheral tolerance and their complete absence leads to autoimmunity in animal models and in human patients with Foxp3 deficiency. CCR4+ Treg cells represent a subset of activated Treg cells and Treg cells capable of migrating to the skin. Specific depletion of Treg cells induced by KW-0761 will provide a unique opportunity to characterize the consequences of Treg cell depletion not only for the tumor growth, but also for systemic immune activation and the homeostasis of a normal tissue. If during the course of treatment with KW-0761 there is a clinical evident focus of skin pathology it will be targeted for biopsy as well as nearby normal skin. Hematoxylin and eosin, CD3, CD4, CD8, FoxP3, CCR4, CD68, and neutrophil elastase stainings will be performed on 4 mm sections.

A relatively recently appreciated modulator of intestinal homeostasis and systemic immunity is the intestinal commensal microbiota. The host immune system and particularly Treg cells are central to maintaining tolerance to commensal microbiota[112,113112,113111,112]. The crosstalk between commensals and local immune cells by Treg can for the first time be investigated in humans with the proposed clinical trial. Fecal specimens will be collected and the intestinal microbiota will be characterized characterized by 454 pyrosequencing of the V1-V3 region of bacterial 16S ribosomal RNA genes. Microbial diversity will be estimated by grouping sequences into operational taxonomic units and calculating the Shannon diversity index. Phylogenetic classification will be obtained using the Ribosomal Database Project classifier. Associations of the microbiota with KW-0761 treatment will be evaluated.

14.3 2 Safety Analyses

Safety data from subjects who have received any portion of KW-0761 will be included in the safety analyses. The frequency and severity of AEs will be tabulated. Baseline, end-of-study, and change from baseline laboratory, vital signs, and ECG parameters will be summarized. Shift tables will be prepared for laboratory parameters. Dot plots or box and whisker plots of selected lab tests over time will be prepared where appropriate. A listing of Baseline and end-of-study concomitant medications will be provided.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction, and entry, data reporting, regulatory monitoring, problem resolution and prioritization and coordination of activities of the protocol study team.

The data collected for this study will be entered into a secure database at MSKCC. Data from this trial will be entered in the Clinical research Database (CRDB). Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSKCC were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at : http://mskweb2.mskcc.org/irb/index/htm.

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Board (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

MSKCC’s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name.
The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1

SAE will be reported to the FDA through the IND Office and the report must include the FDA assigned BB-IDE, BB-IND or IND number and name.

17.2.2 SAE Reporting to Kyowa Hakko Kirin Pharma (KKP)

MSKCC must report all SAEs to Kyowa on a MedWatch 3500A form, or institutional SAE form within five (5) calendar days of the Awareness date. The completed MedWatch/case report should be faxed immediately upon completion to Kyowa Drug Safety at:

KKP Drug Safety Surveillance
Phone: 1-609-919-1100
Available 9:00am-5:00PM (EST)
2:00PM-10:00PM (GMT)
US Fax: 1-800-209-2251
Email address: saesource@kyowa-kirin-pharma.com
Available 24 hours daily

Additional Reporting Requirements to Kyowa include the following:

Any reports of pregnancy following the start of administration with KW-0761 will be transmitted to Kyowa within thirty (30) calendar days of the Awareness Date.

All Non-serious Adverse Events originating from the Study will be forwarded in a Kyowa quarterly report.

17.3 3 Ethical Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the PI, authorized representatives and Investigators abide by GCP as described in International Conference on Harmonization (ICH) guideline E6, and in 21 Code of Federal Regulations (CFR) parts 50, 54, 56, and 312. Compliance with these regulations also constitutes compliance with the ethical principles described in the most recent revision of the Declaration of Helsinki that is recognized by the US FDA and the EMA.

The Investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The Investigator should maintain a list of sub-Investigators and other appropriately qualified persons to whom significant trial-related duties have been delegated.

17.4 Institutional Review Board

The Principal Investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study and retain all of this documentation in the study file. It is also the responsibility of the Principal Investigator to obtain other committee approvals based on the policies of his institution.

Initial IRB approval, and all materials approved by the IRB including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection. The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form.

The Investigator will notify the IRB of deviations from the protocol or any SAE occurring at the site, in accordance with local procedures.

17.5 Audits and Inspections

The Governing Regulatory Authorities, the IRB, and an auditor authorized by the PI may request access to all source documents, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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Appendix 1.

Overall Response using RECIST based immune related response criteria (irRC)

Antitumor response based on total measurable tumor burden.

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5 x 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden:

Tumor Burden = SPD_{index} lesions + SPD_{new}, measurable lesions

Overall response using the irRC.

The overall response according to the irRC is derived from time-point response assessments (based on tumor burden) as follows:

Immune related complete response (irCR): complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Immune related partial response (irPR): decrease in tumor burden ≥30%relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation

Immune related stable disease (irSD): not meeting criteria for irCR or irPR, in absence of irPD

Immune related progressive disease (irPD): increase in tumor burden ≥20% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

An irRC overall response of irCR or irPR requires confirmation by a second (confirmatory) evaluation meeting the criteria for irRC response and performed no less than 4 weeks after the criteria for response are first met.