A Phase I/II Study of Pembrolizumab in Combination with Ibrutinib for Advanced, Refractory Colorectal Cancers

NCT03332498

Version 8.0

September 15, 2018

A Phase I/II Study of Pembrolizumab in Combination with Ibrutinib for Advanced, Refractory Colorectal Cancers

MCC # 19091

Sponsor and Principal Investigator: Richard Kim M.D.
H. Lee Moffitt Cancer Center
12902 Magnolia Drive, Tampa, Florida, 33612
Telephone: 813-745-6898
Fax: 813-745-7229
E-mail: Richard.Kim@moffitt.org

Co-Investigators: Dae Won Kim MD
Rutica Mehta MD

Statistician: Michael Schell, PhD
Michael.Schell@moffitt.org

Protocol Version Date: Sept 15rd, 2018
Protocol Version Number: 8.0

Funding provided by Janssen Scientific Affairs LLC
Study drug (ibrutinib) provided by Janssen Scientific Affair LLC
Study drug (pembrolizumab) provided by Merck Pharmaceuticals

Protocol Synopsis

Title	**A Phase I/II Study of Pembrolizumab in Combination with Ibrutinib for Advanced, Refractory Colorectal Cancers**
Clinical study phase	Phase I/II
Study Agents	Ibrutinib PO Pembrolizumab IV
Background	Colorectal cancer is one of the most common worldwide malignancies, with close to 50% of patients ultimately developing metastatic disease. There remains an urgent need for additional novel options for patients who have disease progression through standard therapies. Pembrolizumab is an anti-PD1 that functions by inhibiting checkpoint inhibition and reversing T cell suppression. It has activity in advanced, refractory colorectal cancer in patients with microsatellite instability but not tumors that are mismatch repair proficient. However, mismatch repair deficient tumors comprise a minority of metastatic colorectal cancers and work is underway to allow a wider application of immunotherapy in this common disease. Ibrutinib is primarily a BTK inhibitor which has been approved for the treatment of several hematologic malignancies. Recent pre-clinical data has shown that there might be a role for ibrutinib in the treatment of solid tumors through counteracting the immune tumor escape mechanism. Because of the immune modulatory function of ibrutinib, it has been suggested that the addition of checkpoint inhibitors could potentially produce a synergistic tumor response. This has been evaluated and confirmed in pre-clinical mouse models of microsatellite stable colorectal cancers.
Rationale	With this pre-clinical rationale, we hypothesize that ibrutinib added to pembrolizumab will be a safe and effective combination in microsatellite stable colorectal cancers.

Study objectives	*Primary Objective (Phase I Portion)* To determine the safety and tolerability, describe the dose-limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) (or the highest protocol-defined dose level in the absence of establishing an MTD) of ibrutinib in combination with pembrolizumab in subjects with advanced, refractory colorectal cancers. *Secondary Objectives (Phase I Portion)*1. To determine the efficacy of ibrutinib in combination with pembrolizumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.12. To determine the efficacy of ibrutinib in combination with pembrolizumab based on the RECIST based immune-related response criteria (irRC) *Primary Objective (Phase II Portion)* To determine the efficacy of ibrutinib in combination with pembrolizumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 *Exploratory Objectives* 1. To use the CancerPlex® panel to assess the neoantigen burden of the tumor. The resulting "immune signature" will be correlated with outcome in a descriptive analysis. 2. To use the Luminex cytokine profiling system to analyze the effect of this combination on the immune system

Indication	Patients with advanced, refractory colorectal cancer
Diagnosis and main criteria for inclusion	• Age ≥18 years of age. • Histologically confirmed diagnosis of colorectal adenocarcinoma • Measurable or non-measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Stage IV or recurrent disease is required. • Patients must have received and progressed through or become intolerant to fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab, and if RAS wild type, cetuximab or panitumumab containing therapies. Prior therapy with regorafenib and/or TAS 102 is allowed • ECOG Performance Score 0 or 1 • Estimated life expectancy > 3 months • Adequate bone marrow, liver and renal function as assessed by the following: o Hemoglobin > 8.0 g/dl o Absolute neutrophil count (ANC) > 1,000/mm3 independent of growth factor support o Platelet count > 100,000/mm3 o Total bilirubin < 1.5 times ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin o AST, ALT and Alkaline Phosphatase ≤2.5 times the ULN (≤5 x ULN for patients with liver involvement) o Creatinine clearance ≥ 30 ml/min
Study design	This is a phase I/II trial using the combination of ibrutinib and pembrolizumab in advanced, refractory colorectal cancer. This will be a 3+3 design with 2 dose cohorts. Following the dose escalation phase, the phase II portion of the study will enroll 32 patients.
Number of subjects	42

Plan for statistical analysis	**Sample Size** The planned sample size is 6-12 patients in the dose-exploration portion (phase I) and 32 patients in the phase II portion. **Phase I** For the dose exploration phase, the number of subjects will depend upon the DLTs observed and the number of dose levels tested as the study progresses in accordance with a 3+3 design. 6-12 patients are expected to be enrolled. Additional subjects could be enrolled if dose de-escalations or expansion of dose exploration is needed. **Phase II** For the phase II portion of this study, the primary endpoint will be disease control rate (CR + PR + SD) at 4 months. Patients will be accrued to the protocol according to a two-stage Minimax design. At least 1 of 18 patients must have disease control at 4 months in the first stage to proceed to the second stage. If the protocol proceeds to the second stage, at least 4 of 32 patients overall must have disease control at 4 months for the therapy to be considered effective We anticipate an attrition rate of 10%, so around 49 patients will be recruited. Based on previous trials, we expect to enroll 42 patients in 12 months.

Table of Contents

1. Introduction

1.1 Background

Colorectal cancer is one of the most common worldwide malignancies,[1] and close to 50% of patients ultimately develop metastatic disease.[2] Over the last few decades, there has been significant progress in the treatment of metastatic disease with the introduction of cytotoxic agents like oxaliplatin and irinotecan as well as biologic agents like bevacizumab and cetuximab. The median survival of those with metastatic disease at diagnosis is now over 2 years. Many patients maintain good performance status even after exhausting standard therapies and there remains an urgent need for additional novel options for these patients.

In the refractory setting, the oral agent regorafenib has been approved based on the results of two phase III studies showing an overall survival (OS) benefit over best supportive care.[3,4] However, drug toxicity is a significant concern, limiting the use of regorafenib. Recently TAS 102, an thymidine-based nucleic acid analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, was approved based on a phase III study demonstrating modest overall survival (1.8 months) improvement against placebo. [5] Once again toxicity (primarily neutropenia and diarrhea) is concerning. New approaches to the management of refractory disease with manageable toxicity represent a clinical unmet need for the majority of patients with advanced colorectal cancer.

1.2 Immunotherapy in colorectal cancer

Tumors contain unique genetic alterations that provide antigens by which they can be identified by the immune system. These antigens should be recognized and killed by T cell receptors.[6] Immune checkpoints are generally activated to allow for self-tolerance and prevent excess autoimmunity. The immune checkpoint inhibitors increase activation of the immune system and recognition of tumor cells for destruction.

Colorectal cancer has long been known to have an immunologic component as tumors with immune infiltration have overall better prognosis.[7] However, immune checkpoint inhibitors and vaccine studies have generally not resulted in significant activity in colorectal tumors.[8,9] Novel approaches using immunotherapy combinations are needed to better target these tumors.

1.3 Ibrutinib

Ibrutinib is primarily a BTK inhibitor which has been FDA approved for the treatment of several hematologic malignancies including CLL, previously treated mantle cell lymphoma, and Waldenstrom's macroglobulinemia, Small lymphocytic lymphoma, Marginal Zone lymphoma and Graft versus host disease. Recent pre-clinical data has shown that there might be a role for ibrutinib in the treatment of solid tumors, including lung and breast cancers.[10,11] Ibrutinib has been hypothesized to counteract the immune escape mechanism used by tumors wherein the Th2 response is promoted and Th1 response (associated with cytotoxicity) is suppressed.[12]

Pre-clinical Experience

Ibrutinib was initially evaluated in hematologic malignancies but has recently been looked at in solid tumors. BTK inhibition by ibrutinib is hypothesized to modulate the tumor microenvironment (Ibrutinib investigator's brochure). In breast cancer lines in vitro, ibrutinib was shown to have an inhibitory effect on tumor growth.[13] In a pancreatic adenocarcinoma model, ibrutinib was found to inhibit tumor growth in vivo.[14] There has also been activity shown in lung cancer cell lines and colon cancer mouse models.[11,15]

Clinical Experience

Clinical Pharmacokinetics
Ibrutinib has been evaluated in human subjects in multiple studies at doses ranging from 140 mg to 840 mg per day. Co-administration of ibrutinib with strong CYP3A inhibitors like ketoconazole has been found to increase exposure of ibrutinib. Based on data for the effects of food, ibrutinib could be taken with or without food at approximately the same time each day.

Clinical Efficacy
Ibrutinib has been FDA approved for the treatment of Chronic Lymphocytic Leukemia, including those tumors with a 17p deletion, previously treated Mantle Cell Lymphoma, and Waldenstrom's Macroglobulinemia based on the results of clinical studies.[16-19]

Clinical Safety
According to the IMBRUVICA USPI (6/2016), the most common adverse reactions (>=20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM) were thrombocytopenia, diarrhea, anemia, neutropenia, musculoskeletal pain, fatigue, bruising, nausea, rash, hemorrhage and pyrexia.The warnings and precautions for ibrutinib include: hemorrhage, infections, cytopenias, atrial fibrillation, hypertension, second primary malignancies, tumor lysis syndrome, embryo-fetal toxicity.

1.4 Pembrolizumab

Human tumors have multiple genetic alterations leading to neoantigens which should be recognized by the immune system of the host. However, cancer can dysregulate immune checkpoint proteins as a way of evading the host immune system and ensuring tumor survival.[20] Immunotherapy in oncology has been evaluated as a means of upregulating the host immune system so that tumors can be recognized as foreign and endogenous anti-tumor immunity can attack tumor cells. Immune checkpoint pathway inhibitors such as anti-CTLA4 and anti-PD-1 antibodies have been evaluated in the treatment of a variety of tumors.

Programmed death 1 is a protein which limits T-cell activity in an effort to minimize autoimmunity.[21] When activated by ligands, PD-1 along with its costimulatory protein B7, decrease T cell activity which can allow tumors to escape immune recognition. Antibodies against PD-1 have been developed in an effort to increase T cell activity.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

Pembrolizumab functions by inhibiting checkpoint inhibition and reversing T cell suppression. A recent study showed activity in advanced, refractory colorectal cancer in patients with microsatellite instability but not tumors that were mismatch repair proficient.[22] The mechanism of action in these tumors is hypothesized to be that the increased immunogenicity of these highly mutated tumors provides multiple targets upon which the anti-PD1 agent can act. However, these tumors comprise only 2-4% of all metastatic colorectal cancers.

Pre-Clinical Experience

Pembrolizumab has been found to enhance T-cell activity in blood cells in vitro (Pembrolizumab Investigator's Brochure). In addition, IL-2 and other cytokine production was enhanced. In addition, it was found to increase the antigen-specific recall response to tetanus toxoid in peripheral blood mononuclear cells from vaccinated individuals in vitro. In vivo, a pembrolizumab like antibody was tested as monotherapy in murine tumor models and found to inhibit tumor growth of a colon adenocarcinoma (Pembrolizumab Investigator's Brochure). In toxicology studies of Cynomolgus monkeys, pembrolizumab at doses up to 200mg/kg weekly or every other week resulted in no treatment related adverse effects.

Clinical Experience

Clinical Pharmacokinetics
Pembrolizumab has been tested in several thousand human subjects with doses ranging from 1mg/kg to 10 mg/kg. Pembrolizumab has been found to have a low potential of eliciting anti-drug antibodies.

Clinical Efficacy
Pembrolizumab has been FDA approved for the treatment of metastatic melanoma and metastatic non-small cell lung cancer based on clinical trial results.[23,24] The majority of responses have been durable and have exceeded 6 months. In melanoma, pembrolizumab has been approved in metastatic disease in the first line setting as well as after progression on ipilimumab or a BRAF inhibitor on patients with a BRAF mutation. In non-small cell lung cancer, it has been approved in advanced disease after progression on one prior treatment in patients whose tumor express PD-L1.

Clinical Safety
The safety profile is similar across tumor types and there has been no pattern of adverse effects with regards to incidence or severity based on dose level. The incidence of drug related adverse effects was generally low and included nausea, fatigue, and diarrhea. Grade 3-5 drug related

adverse events have included anemia increased LFTs, and pulmonary toxicity.

1.5 Rationale

Because of the immune modulatory function of ibrutinib, it has been suggested that the addition of checkpoint inhibitors like pembrolizumab could potentially produce a synergistic tumor response. This was initially evaluated in a mouse model of lymphoma, which showed that anti-PDL-1 therapy alone delayed tumor growth but was not curative. However, the combination of ibrutinib with anti-PDL1 resulted in about 50% of the mice being cured.[25] This combination was then tested in colon and breast cancer mouse models and showed a similar synergistic effect. Interestingly, the colon mouse model (CT26) is not known to be associated with a microsatellite high phenotype.[26] A similar study with the anti-CTLA4 agent ipilimumab showed synergy with ibrutinib, also in a colon mouse model.[27]

As there is known synergy between immunotherapy agents and ibrutinib in microsatellite stable colon mouse models, we hypothesize that ibrutinib added to pembrolizumab will lead to a disease response and improve survival in microsatellite stable colorectal cancers.

The combination of pembrolizumab and ibrutinib is investigational as is for the treatment of colorectal cancer. On the basis of the data described above, we hypothesize that the combination of ibrutinib and pembrolizumab in refractory colorectal cancers will be safe and efficacious.

2. Study Objectives

Primary Objective (Phase I)

To determine safety and tolerability, describe the dose-limiting toxicities (DLTs), and determine the maximum tolerated dose (MTD) (or the highest protocol-defined dose level in the absence of establishing an MTD) of ibrutinib in combination with pembrolizumab in subjects with advanced, refractory colorectal cancers.

Secondary Objectives (Phase I)

1. To determine the efficacy of ibrutinib in combination with pembrolizumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
2. To determine the efficacy of ibrutinib in combination with pembrolizumab based on the RECIST based immune-related response criteria (irRC)..
3. To determine overall survival

Primary Objective (Phase II)

To determine the efficacy of ibrutinib in combination with pembrolizumab based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Exploratory Objective

1. To use the immunohistochemical stains and HTG EdgeSeq ImmunoOncology Assay to assess the host immune response in tumor microenvironment. The resulting "immune gene expression profiles and immune cells profiles" will be correlated with clinical outcome in a descriptive analysis.
2. To use the Luminex Multiplex immunoassay and the flowcytometry, to analyze the effect of this combination on the immune system and immune cells in peripheral blood.

3. Study Design

This is a phase I/II open-label trial to assess the safety, tolerability, and preliminary anti-tumor activity of pembrolizumab and ibrutinib in subjects with advanced, refractory colorectal cancer.

The study consists of two phases:

Escalation phase (Phase I)

The objective of this phase is to investigate the safety, tolerability and recommend the dose of the combination. Ibrutinib and pembrolizumab will be concurrently administered in sequential cohorts of 3- 6 subjects with each receiving pembrolizumab 200 mg every 3 weeks (Q3W) and ibrutinib at doses of 420 mg daily (cohort 0) and 560 mg daily (cohort 1) .

The first cohort will enroll a minimum of 3 subjects, according to a standard 3+3 design. If 0 out of the first 3 subjects in the first cohort experience a dose-limiting toxicity (DLT), then dose escalation will continue as planned. If 1 out of the first 3 subjects experience a DLT, then the cohort will be expanded to a total of 6 subjects, and if no more than 1 out of 6 subjects experiences a DLT in a given dose cohort, dose escalation will continue as planned. If ≥ 2 DLTs are observed in the first dose cohort, the principle investigator will discuss with Janssen on how to proceed. The DLT evaluation period will be defined as the time from the first dose of pembrolizumab and ibrutinib to 42 days after the first dose or if a subject experiences a DLT within this time period. A maximum of 2 cohorts is expected, making a total of approximately 12 evaluable subjects during the dose escalation phase.

Phase II (Phase II)

The phase II portion of the study is to be conducted in patients with advanced, refractory colorectal cancer. The objective of this phase of study is to assess disease control rate (CR + PR+ SD) and further investigate the safety, tolerability and preliminary clinical activity of the combination at the recommended dose. 32 evaluable subjects with advanced, refractory colorectal cancer will be enrolled. Patients will be on treatment until unacceptable toxicity or disease progression for a maximum of 24 months.32 subjects with microsatellite stable colorectal cancer will receive concurrent ibrutinib PO qdaily and pembrolizumab 200 mg IV Q3W beginning on Day 1 using the recommended dose of ibrutinib from the escalation phase to evaluate disease control rate and further evaluate safety, tolerability and preliminary evaluation

of clinical efficacy. Initiation of expansion arms with the recommended dose of ibrutinib in combination with pembrolizumab at 200 mg IV will be based on an adequate safety and tolerability profile of the combination from the escalation phase.

4. Eligibility

4.1 Inclusion Criteria

- Histologically confirmed diagnosis of colorectal adenocarcinoma
- Measurable or non-measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Stage IV or recurrent disease is required.
- Patients must have received and progressed through or become intolerant to fluoropyrimidine, irinotecan, oxaliplatin, and bevacizumab. If RAS wild type, patients should have received and progressed or become intolerant to the above as well as cetuximab or panitumumab containing therapies. Prior therapy with Regorafenib and/or TAS 102 is allowed
- ECOG Performance Score 0 or 1
- Estimated life expectancy > 3 months
- Adequate bone marrow, liver and renal function as assessed by the following:
  o Hemoglobin > 8.0 g/dl
  o Absolute neutrophil count (ANC) > 1,000/mm3 independent of growth factor support
  o Platelet count > 100,000/mm3
  o Total bilirubin < 1.5 times ULN unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin
  o AST, ALT and Alkaline Phosphatase ≤2.5 times the ULN (≤5 x ULN for patients with liver involvement)
  o Creatinine clearance ≥ 30 ml/min
- Patients must not have had chemotherapy, major surgery, monoclonal antibody therapy or experimental therapy within the 21 days prior to the start of ibrutinib administration
- Women of childbearing potential must have a negative serum orurine pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 4 months for both females and males after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Subjects (men and women) must agree to not donate sperm (males) or eggs (females) during and up to 120 days after the last dose of study treatment.
- Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure. Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other study requirements.

4.2 **Exclusion Criteria**

- Subjects with active CNS metastases are excluded. If CNS metastases are treated and subjects are at neurologic baseline for at least 2 weeks prior to enrollment, they will be eligible but will need a Brain MRI prior to enrollment. Subjects must be off corticosteroids or on a dose of less than 10mg per day.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways).
- Prior therapy with ibrutinib or other BTK inhibitors.
- Previous or concurrent cancer within 3 years prior to treatment start EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer, superficial bladder tumors [Ta (non-invasive tumor), Tis (carcinoma in situ) and T1 (tumor invades lamina propria)].
- Known history of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS).
- Serologic status reflecting active hepatitis B or C infection. Patients who are hepatitis B core antibody positive and who are antigen negative, will need to have a negative PCR result prior to enrollment. Those who are hepatitis B antigen positive or PCR positive, will be excluded.
- Subjects with Child Pugh B or C cirrhosis.
- History of severe hypersensitivity reactions to other monoclonal antibodies
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
- History or concurrent condition of interstitial lung disease of any grade or severely impaired pulmonary function.
- Unresolved toxicity higher than CTCAE grade 1 attributed to any prior therapy or procedure, excluding alopecia.
- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmia, congestive heart failure, any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or history of myocardial infarction within 6 months prior to first dose with study drug

- Unable to swallow capsules or disease significantly affecting gastrointestinal function and/or inhibiting small intestine absorption such as; malabsorption syndrome, resection of the small bowel, or poorly controlled inflammatory bowel disease affecting the small intestine.
- Requires anticoagulation with warfarin or equivalent vitamin K antagonists (e.g. phenprocoumon).
- Requires treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor.
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.
- Major surgery or a wound that has not fully healed within 4 weeks of enrollment.
- Vaccinated with live, attenuated vaccines within 4 weeks of enrollment
- Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis within 6 months

Excluded Therapies and Medications for Cancer

- Anticancer chemotherapy during the study or within 4 weeks of study enrollment. Subjects must have recovered from the toxic effects of the previous anti-cancer chemotherapy (with the exception of alopecia). Anti-cancer therapy is defined as any agent or combination of agents with clinically proven anti-tumor activity administered by any route with the purpose of affecting the malignancy, either directly or indirectly, including palliative and therapeutic endpoints.
- Hormonal therapy during the study or within 2 weeks of first study enrollment.
- Radiotherapy to target lesions during study or within 2 weeks of enrollment.
- An irradiated lesion is considered evaluable only if it has shown enlargement since the completion of last radiation.
- Bone marrow transplant or stem cell rescue.
- Investigational drug therapy outside of this trial during or within 4 weeks of first study treatment.

4.3 Withdrawal of Subjects from Study

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a

subject may decline to participate further. The subject will not suffer any disadvantage as a result.

- Pregnancy. Pregnancies will be reported to Janssen and Merck within 24 hours of having knowledge of the event. Pregnancy will not be reported as an SAE but the subject must be withdrawn from the trial immediately. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Subject is lost to follow-up.
- Death.

All subjects who discontinue should comply with protocol specified follow-up and survival procedures. The ONLY exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form page.

Subjects **may be** withdrawn from study treatment for the following reasons:

- The subject is non-compliant with ibrutinib administration as measured by a dosing diary, pembrolizumab administration, or trial procedures; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to ibrutinib or pembrolizumab.
- The development of a second cancer.
- Development of an illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 3 or 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Any subject with progression of disease will come off of treatment except for patients deriving clinical benefit as deemed by the principal investigator with a maximum of 24 months on therapy. In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

4.3.1 Screen Failures/Dropouts/Replacements

A subject who discontinues study participation prematurely for any reasons except death, disease progression and severe toxicity is defined as a dropout. A subject who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see above) is regarded a “screening failure”. Subjects who withdraw from treatment (for any reason) during dose seeking phase may be replaced. Patients will be

considered inevaluable for the primary endpoint of disease control rate if they do not have at least one post-baseline disease response assessment. Inevaluable patients may be replaced.

4.3.2 Removal of Patients from Protocol Therapy

Patients will be removed from study when any of the criteria listed

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable AE(s)
- Patient decides to withdraw from the study **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Notify the Principal Investigator and document the reason for study removal and the date the patient was removed in the eCRF. The patient should be followed per protocol

5. Treatment Plan

5.1 Drug Administration

Ibrutinib
Ibrutinib should be administered orally once daily with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. Ibrutinib must not be taken with grapefruit juice or Seville orange juice
Ibrutinib drug product is a white opaque, size 0, hard gelatin capsule marked with "ibr 140 mg" in black ink, containing 140 mg of ibrutinib. Ibrutinib capsules are supplied in a white HDPE bottle with a child-resistant closure containing 90 or 120 hard capsules.Keep ibrutinib out of the sight and reach of children.

Ibrutinib Capsules, 140 mg should be stored according to the storage conditions indicated on the label. The recommended storage condition for ibrutinib capsules is 15°C to 25°C (59°F to 77°F) with excursions permitted to 30°C (86°F).

Pembrolizumab
Pembrolizumab is provided as a white to off white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only.

Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2 to 8°C).

The lyophilized drug product after reconstitution with sterile water for injection, and the liquid drug product are a clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration. The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted MK-3475 solutions in the IV bags.

Treatment

Treatment will be administered on an outpatient basis. For ibrutinib a self-report pill diary will be utilized to report medication adherance. Reported AEs and potential risks are described in Section 8. Dose delays for ibrutinib and pembrolizumab are described in Section 5.1.6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. The starting dose of ibrutinib will be 420 mg daily, taken orally. The dose of pembrolizumab is fixed at 200 mg IV over 30 minutes every 3 weeks. Each cycle will last for 3 weeks.

Subjects will be enrolled in 3 + 3 design with 3-6 subjects per cohort to ensure a minimum of 3 and a maximum of 6 evaluable subjects per cohort. It is estimated that two cohorts will be needed during the dose escalation phase of the study as follows:

Dose Escalation Schedule		
Cohort	**Dose**	
	Ibrutinib	**Pembrolizumab**
0	420 mg PO qdaily	200 mg IVover 60 min q3wk
1	560 mg PO qdaily	200 mg IV over 60 min q3wk

Based on current available data, the ibrutinib starting dose will be 420 mg (Cohort 0). Ibrutinib dose could be escalated to 560 mg (Cohort +1) based on the safety and tolerability profile of the combination in Cohort 0. If DLT is seen with Cohort 0, the principal investigator will re-evaluate and discuss with Janssen and Merck on how to proceed.

Each subject will receive ibrutinib daily and pembrolizumab Q3W continuously and will undergo assessments for safety (DLTs, AEs, vital signs, clinical laboratory tests, ECOG performance status, and physical examinations) according to the schedule of assessments.

The DLT evaluation period will be defined as the time from the first dose of ibrutinib or pembrolizumab to 42 days (2 cycles) after the first dose or if a subject experiences a DLT within this time period. The total duration of dose interruptions for ibrutinib will be up to 6 days (intermittent or continuously), during a period of 42 days without a subject being deemed

inevaluable.

Rules for dose escalation and de-escalation are as follows:

1. A minimum of 3 evaluable subjects will be enrolled in each dose cohort. The administration of ibrutinib and pembrolizumab to the first and second subjects of each cohort will be separated by at least 72 hours. Providing there are no serious or unexplained safety issues, dosing of the remainder of the cohort will continue as suitable subjects are identified. All safety data will be reviewed before proceeding with an escalation or de-escalation decision.

2. A 3+3 dose-escalation design will be followed as summarized below:

– If 0 out of the 3 evaluable subjects in a dose cohort experience a DLT during the DLT evaluation period, dose escalation may proceed to the next planned cohort.
– If 1 of the 3 evaluable subjects in any dose cohort experiences a DLT during the DLT evaluation period, that dose cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose cohort experiences a DLT, dose escalation may proceed to the next planned dose cohort.
– If 2 or more subjects in a dose cohort experience a DLT during the DLT evaluation period, the MTD will have been exceeded and no further subjects will be enrolled into that dose cohort.

There will be no intra-subject dose escalations.

5.1.1 Rationale for Flat Dose Regimen of Pembrolizumab

An open-label Phase I trial was conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. No MTD has been identified to date. In pharmacokinetic studies, the relationship between clearance and body weight is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe. A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

5.1.2 Definition of dose-limiting toxicity

A DLT is defined as any toxicity not attributable to the disease or disease-related processes under investigation, which occurs from the start of combination (post dose Day 1 Cycle 1) up to 42 days and is considered by the Investigator to be definitely, probably, or possibly related to the treatment. A DLT will be defined as any Grade 3 or higher treatment-related toxicity that occurs during the DLT evaluation period, including:

1. Any Grade 4 immune-related AE (irAE) irrespective of duration

2. Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration

3. Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade ≤ 2 within 3 days after onset despite maximal supportive care including systemic corticosteroids or downgrade to Grade ≤ 1 within 14 days after onset of the event.

4. Any $\geq$ Grade 2 pneumonitis or interstitial lung disease (ILD) that does not resolve to grade 1 within 3 days of the initiation of maximal supportive care
5. Liver transaminase elevation higher than 10 × upper limit of normal (ULN) or total bilirubin higher than 5 × ULN **that lasts for longer than 7 days**. Any grade 3-4 non hematologic toxicity which does not resolve within 4 days will be considered a DLT.

A DLT excludes the following conditions:

1. Vitiligo or alopecia of any grade.
2. Isolated laboratory changes of any grade without clinical sequelae or clinical significance.
3. Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
4. Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.) that resolves to $\leq$ Grade 1 within 30 days. Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. However isolated laboratory changes of any grade without clinical sequelae or clinical significance are not considered DLTs.

5.1.3 Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable subjects experience a DLT at a dose level. Once the non-tolerated dose is defined the MTD will be confirmed at the previous dose-level below the non-tolerated dose or a dose between the non-tolerated dose and the last tolerated dose may be investigated. Six evaluable subjects are required to determine the MTD.

5.1.4 Definition of evaluable subject

For decisions on dose escalation, an evaluable subject is defined as a subject that meets all of the following criteria:

- Has received ibrutinib at the protocol-specified dose for at least 36 out of first 42 days of combination therapy
- Has received one infusion of pembrolizumab at the protocol-specified full dose during the first 42 days of therapy
- Has completed the minimum safety evaluation requirement which is defined as the time from consent to 42 days after the first dose.

OR

- Has experienced a DLT any time during the first 42 days of combination therapy.

5.1.5 Dose Modifications for Treatment-Related Toxicity

All toxicities will be graded according to National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) (NCI CTCAE v 4.03).

Phase I:

No dose modifications will be allowed in the escalation phase during the DLT evaluation period.

If a subject experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required.

Phase II:

Dose reductions for AEs related to ibrutinib will be performed as per Table 1 below.

Dose modifications will not be required for AEs that are clearly not attributed to ibrutinib or pembrolizumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Dosing may continue despite concurrent vitiligo of any AE grade.

If a subject experiences a clinically significant and/or unacceptable toxicity, dosing will be interrupted and supportive therapy administered as required.

5.1.6 Dose Delays for Treatment-Related Toxicity

Toxicity that occurs during the expansion phase should be classified as drug related or non-drug related. Attribution of toxicity is at the discretion of the principal investigator. The study investigator will determine if either or both medications should be held.

Table 1: Criteria for Dose Delays in Case of Suspected Ibrutinib Toxicity

Non-hematologic toxicity	Actions
Grade 3 or greater	• Interrupt ibrutinib until recovery to grade ≤1. • Then reintroduce ibrutinib at same dose. • If the toxicity reoccurs, reduce dose by one capsule • A second dose reduction of 140 mg may be considered if needed • If toxicity remains despite two dose reductions, discontinue ibrutinib

Hematologic toxicity	Actions *Note: Growth factors, including platelets and GCSF, will not be administered prophylactically but may be prescribed at the discretion of the treating physician*
Grade 4	• Interrupt ibrutinib until recovery to grade ≤1. • Then reintroduce ibrutinib at same dose. • If the toxicity reoccurs, reduce dose by one capsule • A second dose reduction of 140 mg may be considered if needed • If toxicity remains despite two dose reductions, discontinue ibrutinib
Grade ≥3 Neutropenia (neutrophils <1,000/mm^3, ≥500 /mm^3) with infection or fever	• Interrupt ibrutinib until recovery to grade ≤1. • Then reintroduce ibrutinib at same dose. • If the toxicity reoccurs, reduce dose by one capsule • A second dose reduction of 140 mg may be considered if needed • If toxicity remains despite two dose reductions, discontinue ibrutinib

Table 2: Criteria for Dose Delays in Case of Suspected Pembrolizumab Toxicity

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

5.2 Concomitant therapy

• All patients should be maintained on the same medications throughout the study period, as medically feasible;
• The investigator should instruct the patient to notify the study staff about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded in the EMR
• Administration of pegfilgrastim or filgrastim following initiation of protocol therapy is at investigator's discretion for all patients;
• Administration of erythropoietin or darbopoietin is allowed;
• Patients must be instructed not to take any additional medications (including herbal supplements and over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded in the EMR If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded;
• In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics or steroids), with the following exceptions:

- CYP3A Inhibitors/Inducers
    - Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.
    - Strong inhibitors of CYP3A (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) should be avoided
    - If a strong CYP3A inhibitor (see Appendix A) must be used in the short term, ibrutinib will be held for the duration of inhibitor use. Subjects will be monitored more closely for signs of ibrutinib toxicity (at the investigator's discretion). No dose adjustment is required in combination with mild inhibitors.
    - Grapefruit and Seville oranges should be avoided during ibrutinib treatment, as these contain moderate inhibitors of CYP3A
    - Avoid use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.
    - A comprehensive list of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

- Anti-platelet Agents and Anticoagulants:
    - Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.
    - Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 5.3.

- Patients who need to be on anticoagulant therapy during treatment with ibrutinib should be treated with low molecular weight heparin as the preferred therapy.
- Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding.

5.2.1 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab or ibrutinib
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

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

5.3 Supportive Care Guidelines for Ibrutinib

The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, and WM) were neutropenia, thrombocytopenia, diarrhea, anemia, musculoskeletal pain, rash, nausea, bruising, fatigue, hemorrhage, and pyrexia. Listed below are guidelines on how to manage these common toxicities.

- **Hemorrhage:** Fatal bleeding events have occurred in patients treated with ibrutinib. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and

petechiae, occurred in approximately half of patients treated with ibrutinib. The mechanism for the bleeding events is not well understood.

- For any planned surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

- For planned minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

- For planned minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

- For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure, or at the discretion of the investigator.

- **Infections:** Fatal and non-fatal infections have occurred with ibrutinib therapy. Grade 3 or greater infections occurred in 14% to 29% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Evaluate patients for fever and infections and treat appropriately per current guidelines.
- **Cytopenias:** Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) based on laboratory measurements occurred in patients treated with single agent ibrutinib. Monitor complete blood counts at least monthly.
- **Atrial Fibrillation:** Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with ibrutinib, particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset dyspnea should have an ECG performed. Atrial fibrillation should be managed appropriately, and if it persists, consider the risks and benefits of ibrutinib treatment and follow dose modification guidelines per the USPI for ibrutinib.
- **Hypertension:** Hypertension (range, 6 to 17%) has occurred in patients treated with ibrutinib with a median time to onset of 4.6 months (range, 0.03 to 22 months). Monitor patients for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.
- **Second Primary Malignancies:** Other malignancies (range, 5 to 16%) including non-skin carcinomas (range, 1 to 4%) have occurred in patients treated with ibrutinib. The

most frequent second primary malignancy was non-melanoma skin cancer (range, 4 to 13%).

- **Tumor Lysis Syndrome:** Tumor lysis syndrome has been infrequently reported with ibrutinib therapy. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.
- **Embryo-Fetal Toxicity:** Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryofetal toxicity including malformations at exposures that were 2-20 times higher than those reported in patients with MCL, CLL/SLL or WM. Advise women to avoid becoming pregnant while taking ibrutinib and for 1 month after cessation of therapy. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

5.5 Management of Immune Related Adverse Events related to Pembrolizumab

5.5.1 Pneumonitis:

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.5.2 Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.5.3 Type 1 diabetes mellitus (T1DM)

If new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

- For T1DM or Grade 3-4 Hyperglycemia: Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.5.4 Hypophysitis:

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.5.5 Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):

- In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
- In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

Grade 3-4 hyperthyroidism

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to **Grade 1 or less**, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.5.6 Hepatic:

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

5.5.7 Renal Failure or Nephritis:

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.5.8 Management of Pembrolizumab Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6 Blinding

This is an open-label trial. There will be no randomization or blinding.

5.7 **Drug Logistics and Accountability**

All study drugs will be stored at the investigational site in accordance with good clinical practice (GCP) and GMP requirements and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiration dates can be found in Dr. Kim's study file; the site-relevant elements, of this information will be available in the ISF. The responsible site personnel will confirm receipt of study drugs and will use the study drugs only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drugs must be properly documented according to Moffitt Cancer Center protocol.

6. Visit schedule and Assessments

6.1 **Screening First Visit**

Screening examinations will only be performed after having received the subject's written informed consent.

The following examinations will be performed within 28 days prior to the first treatment:

- Written subject informed consent to be obtained prior to any screening assessments.
- Complete medical history and physical examination, including demographics, surgery, therapies, medications, smoking, alcohol history, co-existing diseases, allergies, NYHA classification, vital signs (heart rate, respiration rate, temperature, and BP), weight and review of systems.
- Medical history ECOG Performance Status Assessment
- 12-lead ECG
- Radiologic assessment: CT scan or MRI (chest, abdomen, pelvis) with tumor measurement by RECIST V1.1 and irRC criteria
- Coagulation (PT-INR and aPTT)
- Hematology (hemoglobin, HCT, RBC, WBC count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), creatine kinase, lipase, amylase, glucose, calcium phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, blood

urea nitrogen (BUN), total protein and albumin

- TSH, free T4
- [redacted]
- Carcinoembryonic antigen (CEA)
- Serum/urine pregnancy test (if applicable)
- Screening for Hepatitis B and C
- Urinalysis including blood, glucose, protein, specific gravity
- [redacted]

6.2 Cycle 1 Day 1

- History and assessment to include physical examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Baseline Toxicity/AE assessment after first dose
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, LDH, creatine kinase, lipase, amylase glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin

6.3 Cycle 2 day 1 and subsequent cycles (max of 32 cycles)

- History and assessment to include brief examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Toxicity/AE assessment
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, LDH, creatine kinase, lipase, amylase glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, BUN, total protein and albumin
- Pregnancy test will be performed at baseline for WOCBP and then only as clinically indicated
-

6.4 Start of every 3rd cycle (Cycle 3, Cycle 6, etc.)

- Radiologic assessment: CT scan or MRI (chest, abdomen, pelvis) with tumor measurement and disease assessment of non-measurable diseaseaccording to RECIST 1.1 and irRC criteria (please see Appendix B)
- TSH and free T4
- Carcinoembryonic antigen (CEA)

- [redacted]

6.5 End of Treatment Visit and Follow up

End of Treatment Visit

The end of treatment visit should be conducted when it is confirmed by the investigator that the patient will receive no further doses of drug on study.

- History and assessment to include brief examination, vital signs (heart rate, respiration rate, temperature and BP) and review of systems
- Toxicity/AE assessment
- ECOG Performance Status Assessment
- Hematology (hemoglobin, HCT, RBC, WBC with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count
- Chemistry (ALT, AST, AP, total bilirubin, direct bilirubin, LDH, creatine kinase, lipase, amylase glucose, calcium, phosphate, magnesium, bicarbonate, sodium
- Radiologic assessment: CT scan or MRI (chest, abdomen, pelvis) with tumor measurement and disease assessment of non-measurable diseaseaccording to RECIST 1.1 and irRC criteria (please see Appendix B) may be conducted if it has not been performed within the last 4 weeks.

Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 30 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase for 24 months and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.6 Calendar

	Screening within 28 days of C1D1	**Cycle 1 Day 1 ± 2 days**	**Cycle 2 day 1 ± 2 days and subsequent cycles**	**Cycle 3 day1 ± 5 day and every 3rd cycle thereafter**	**EOT[m]**	**Safety Follow-Up Visit ± 7 days[n]**	**Post-Progression Follow-up[j]**

Complete History/Physical[a]	X				X		
History & Assessment [b]		X	X			X	
Toxicity Notation		X	X		X	X	
ECOG	X	X	X		X	X	
ECG	X						
Tumor Measurement/Disease Assessment[c]	X			X	X		
Hematology[d]	X	X	X		X		
Chemistry[e]	X	X	X		X		
Coagulation[f]	X						
Urinalysis[g]	X						
TSH, free T4	X			X			
CEA	X			X			
Hepatitis Screening [h]	X						
Serum/urine Pregnancy, if applicable [i]	X						
Survival f/u [j]							X
[redacted]	[redacted]						
[redacted]	[redacted]			[redacted]			

a. *Complete medical history and physical examination* including demographics, surgery, therapies, medications, smoking, alcohol history, co-existing diseases, allergy, NYHA classification, vital signs (heart rate, respiration rate, temperature and BP), height, weight and review of systems. A full physical exam should be performed during screening.

b. *History and assessment* including brief examination, vital signs and review of systems. Note all toxicities and adverse events, using CTCAE version 4.03 and in accordance with section 9.1. The investigator or qualified designee will also perform a directed physical exam as clinically indicated prior to each treatment cycle administration.

c. Tumor assessment using CT or MRI (chest, abdomen, pelvis) (at investigator's discretion) will be collected at screening, after every 3 cycles, and as clinically indicated. Tumor response will be assessed using RECIST 1.1 and irRC criteria**.** Tumor measurement/disease assessment should be performed within 7 days at the beginning of every 3rd cycle.

d. Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils) and platelet count.

e. ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, creatine kinase, lipase, amylase, glucose, calcium, phosphate, magnesium, bicarbonate, sodium, potassium, chloride, creatinine, blood urea nitrogen (BUN), total protein and albumin.

f. PT-INR and aPTT.
g. Urinalysis including blood, glucose, protein, specific gravity
h. Hepatitis B surface antigen, surface antibody, and Hepatitis C antibody
i. Pregnancy test will be performed at baseline for WOCBP and then only as clinically indicated
j. After off treatment following disease progression survival f/u, can be performed over the phone every 3 months
k. Archival tissues (10 unstained slides) if available
l. The PBMC should be viably frozen (for flow cytometric analysis) and the plasma frozen separately .The actual analyses used will be based on response and determined by the investigator at a later date. Two green top (Sodium Heparin) tubes (about 20 ml) will be used each time. This will ONLY be collected at the screening and at the beginning of the 3rd cycle.
m. If a subject discontinues treatment due to confirmed PD, only the EOT disease assessment is required if it has been > 4 weeks since the last disease assessment
n. The safety follow-up visit will be approximately 30 days after the last dose or prior to the start of a subsequent anti-cancer therapy.

7. Assessment types

7.1 Pre-Treatment Assessments

The nature of the study and the associated potential risks will be explained to all study candidates and a signed informed consent must be obtained before any study-specific Pre-Treatment procedures are performed. Pre-Treatment assessments must be completed and reviewed within 28 days prior to the start of study drug treatment to ensure eligibility for study entry

Pre-Treatment evaluations will include inclusion/exclusion criteria evaluation, demographic data collection, ECOG performance status, NYHA classification, medical and surgical history collection, vital signs, complete physical examination (including height and weight), 12-lead ECG, biochemistry, hematology and urinalysis, pregnancy test (urine or serum β- hCG in women of childbearing potential only), and tumor assessments

7.2 Efficacy

Response and progression will be evaluated using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (see Appendix B). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

7.3 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, ECG and the regular monitoring

of vital signs, and physical condition as shown in corresponding tables. Safety and tolerability will be assessed according to the NIH/NCI CTC version 4.0.

8. Safety monitoring and reporting

8.1 Adverse Events

8.1.1 Definitions

An Adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy. Clinically significant laboratory results are those requiring a change in the patient's treatment, further diagnostic testing or specific clinical intervention (i.e., treatment delays or dose modifications, etc). The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated by the investigator to determine:

• the severity grade (mild, moderate, severe) or (grade 1-4)

• its relationship to either or the study drugs (unrelated, unlikely, possible, probable, definite)

• its duration (start and end dates or if continuing at final exam)

• action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)

• whether it constitutes a serious adverse event (SAE)

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:
• Definite: The AE is clearly related to the study treatment;
• Probable: The AE is likely related to the study treatment;
• Possible: The AE may be related to the study treatment;
• Unlikely: The AE is doubtfully related to the study treatment;
• Unrelated: The AE is clearly not related to the study treatment.

A serious adverse event is an undesirable sign, symptom or medical condition which:

1. Is fatal or life-threatening.
2. Requires or prolongs hospitalization.
3. Results in persistent or significant disability/incapacity.

4. Constitutes a congenital anomaly or a birth defect.
5. Is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

For full adverse event reporting as per Janssen guidelines, see **Appendix C.**

Events not considered to be serious adverse events are hospitalizations for the:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Serious adverse event reporting is initiated after the signs informed consent, and continues until 4 weeks after the patient's last dose of study medication. The period after discontinuing study drug may be extended at investigators discretion.

Progression of the cancer under study is not considered an adverse event.

8.1.2 Adverse Events of Special Interest (AESI) with Ibrutinib

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to Janssen Drug Safety per the SAE reporting timelines.

Major Hemorrhage
Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or which results in one of the following:

(1) Intraocular bleeding causing loss of vision,
(2) The need for a transfusion of 2 or more units of red cells,
(3) Or an equivalent

All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03. Events meeting the definition of major hemorrhage will be captured as an event of special interest.

Intracranial Hemorrhage
Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.

Other Malignancies
In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival

8.2 Safety Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assessed according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.03) that is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

The principal investigator will monitor the data and toxicities to identify trends and will be responsible for revising the protocol as needed to maintain safety. Serious adverse events will be reported to the IRB in accordance with IRB and Moffitt institutional policies and to the FDA as described below. The Protocol Monitoring Committee (PMC) at Moffitt monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators will provide to the PMC the following information for data and safety monitoring: statistical report of the study's progress, summary of adverse events and deviations. Safety and monitoring reports are to be submitted to the PMC after completing each odd numbered dose level (i.e., 1,3,5, etc), or more frequently if requested by the PMC. A final safety and monitoring report must be submitted to the PMC within three months of defining the maximum tolerated dose (MTD).

8.2.1 Internal Monitoring Plan

The trial will be monitored per Moffitt Cancer Center policy MRI-P.PSO.03, *Monitoring of Investigator Initiated Clinical Research.* Data will be captured in Oncore, Moffitt's Clinical Trials Management System, Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice, and applicable regulatory requirements.

8.3 Reporting of Serious Adverse Events

Moffitt Cancer Center will report SAEs within 24 hours of the study team becoming aware of the event by completing an SAE report in OnCore, the clinical trial management system.

The definition of serious adverse events (SAEs) is given in Section 8.1.1.

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned

grade 4, according to CTCAE definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTCAE grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

Reporting Serious Adverse Events (SAEs) to the FDA
Any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. SAEs may be reportable to the FDA for both FDA-approved (post-market) drugs as well as investigational agents.
For an event to be reportable to the FDA, it must meet ***both*** of the following requirements as determined by the principal investigator of the study:
1. The event is possibly, probably or definitely ***related*** to the agent
2. The event is ***unexpected*** (i.e., not listed in the protocol, investigational brochure, or informed consent)

Expedited reporting to the FDA on a MEDWatch 3500A form will be used for all unexpected and related serious adverse events as defined in 21 CFR 312.32.
The current MedWatch mandatory reporting form FDA 3500A can be found on the FDA website:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
Use: Form FDA 3500A - Mandatory Reporting
Complete the ***MedWatch*** report and mail it to the appropriate address below (please also see **FDA reporting fax number** under section 7.4.2):
For Drugs:
Central Document Room Center for Drug Evaluation and Research Food and Drug Administration 5901-B Ammendale Road Beltsville, MD 20705-1266

To report an event for an INVESTIGATIONAL AGENT under investigational new drug applications:
Send a narrative of the event with circumstances, IND number, and why it is related and unexpected to the H. Lee Moffitt Cancer Center Regulatory Affairs IND Office. A MedWatch report for the event would suffice. The Regulatory Affairs IND Office at Moffitt Cancer Center will submit the reportable event as an IND safety report to the FDA on behalf of the principal investigator.
If applicable, the site should also follow protocol guidelines for additional reporting to government agencies.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to Merck and Janssen within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures. The completed Medwatch/case report should be faxed immediately upon completion to the below:

Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)
Janssen Drug Safety: (IIS-BIO-VIRO-GCO@its.jnj.com) or by fax if email is unavailable (866-651-0219).

The Investigator may report serious adverse events (SAEs) as described below.

A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be faxed to:

PPD/PVG
United States and Canada: Toll-Free Fax: 1-888-529-3580
Rest of World: Toll-Free Fax: 93581-888-529-3580 (will automatically connect to

PVGs toll-free safety fax number (1-888-529-3580)

8.4 Pregnancies

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Principal Investigator. Within 24 hours of the Investigator becoming aware, the pregnancy must be reported to:

Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)
Janssen Drug Safety: Janssen Secure Email (IIS-BIO-VIRO-GCO@its.jnj.com) or by fax if email is unavailable (866-651-0219).

9. Statistical Methods and Data Analysis

9.1 Definition of Study Endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and Tolerability (Phase I)
- Disease control rate (CR + PR+ SD) at 4 months (Phase II)
- Tumor response by RECIST 1.1 and irRC (Secondary)
- Exploratory biomarkers, including genetic sequencing and cytokine multiples assay (Exploratory)

9.2 Determination of sample size

The primary objective of the phase I portion of this study is to investigate the safety and tolerability and thereby identify the recommended dose of ibrutinib in combination with pembrolizumab for evaluation in future clinical studies. Hence the number of subjects has been based on the desire to obtain adequate tolerability, safety and pharmacodynamic data while exposing as few subjects as possible to the investigational product and procedures.

For the dose escalation phase of the study, cohorts of 3-6 evaluable subjects (who have either failed to respond or relapsed following standard treatment, were unable to tolerate, or were not eligible for standard treatment) will be required. The total number of subjects will depend upon the number of dose escalations necessary.

For the phase II portion of the study, 32 patients will be accrued. The primary endpoint of this portion is disease response (CR+ PR+ SD) at 4 months.

Patients will be accrued to the protocol according to a two-stage Minimax design. [28] Based on patient disease control at 4 months (CR + PR + SD), we will either conclude that the therapy is effective or ineffective. The two-stage design has the smallest maximum sample size with the following two properties:

(1) if the true disease control rate is less than or equal to 5%, we will conclude that the therapy is ineffective with probability of at least 0.90 (alpha = 0.10), and
(2) if the true disease control rate is at least 20%, we will conclude that the therapy is effective with probability at least 0.90 (beta = 0.10).

At least 1 of 18 patients must have disease control at 4 months in the first stage to proceed to the second stage. If the protocol proceeds to the second stage, at least 4 of 32 patients overall must have disease control at 4 months for the therapy to be considered effective.Six patients treated at the MTD will be counted for disease control in the phase II portion of the study if the treatment plan or the eligibility criteria does not change.

9.3 Analysis Sets

All subjects who receive at least one dose of the study medication will be included in the safety evaluation.

All subjects who undergo at least one staging reassessment will be used for efficacy evaluations.

9.4 Statistical and analytical plans

9.4.1 Demographic and other baseline characteristics

Demographics and baseline characteristics will be summarized by cohort and by treatment. Quantitative data will be summarized by descriptive statistics. Frequency tables will be provided for qualitative data.

9.4.2 Adverse Events

Individual listings of AEs will be provided. The incidence of treatment-emergent AEs and drug-related AEs, respectively, will be summarized by cohort by treatment by worst NCI CTC grade.

9.5 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, and vital signs. These will be collected for all subjects. Appropriate summaries of these data will be presented as described in Section 9.8. All subjects who received at least 1 dose of pembrolizumab or ibrutinib will be eligible.

9.6 Calculation or derivation of tumor response variables

At each visit subjects will be programmatically assigned a RECIST and irRC visit response of CR, PR, SD or PD depending on the status of their disease compared to baseline and previous assessments. See Appendix B.

9.7 Methods of Statistical Analysis

The statistical analyses will be performed by the Biostatistics Group at Moffitt Cancer Center. Data from the dose escalation phase (phase I) and the dose expansion phase (phase II)) will be presented separately.

Demographic data
Characteristics of the subjects, including medical history and disease characteristics at baseline will be listed for each subject and summarized by dose group and expansion phase arm. A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.

Reasons for discontinuation of investigational product will be listed including the study day of treatment discontinuation and will be summarized by dose group and expansion phase arm.

Exposure
Exposure to investigational product (i.e., total amount of study drug received) will be listed for all subjects.

Total exposure and total time on study (date of last dose minus date of first dose) will be summarized with descriptive statistics. In addition, the number and percentage of subjects with at least one dose interruption/dose delay and at least one dose reduction will be presented separately for the initial period of evaluability defined as 28 days and for any time following this

initial period of the study.

Safety
Safety data will not be formally analyzed. All subjects who receive at least one dose of ibrutinib or pembrolizumab will be included in the assessment of the safety profile (safety analysis set). At the end of the study, appropriate summaries of all safety data will be produced, as defined below.

Data from all cycles of initial treatment will be combined in the presentation of safety data. AEs will be listed individually by subject and dose group/expansion phase arm. For subjects who have a dose modification, all AEs (due to drug or otherwise) will be assigned to the initial dose group. The number of subjects experiencing each AE will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and CTCAE grade. The number and percentage of subjects with adverse events in different categories (e.g., causally related, CTCAE grade ≥3 etc.) will be summarized by dose group/expansion phase arm, and events in each category will be further summarized by MedDRA system organ class and preferred term, by dose group. SAEs will be summarized separately if a sufficient number occur.

Any AE occurring before the first dose of investigational product (i.e., before study Day 1) will be included in the data listings but will not be included in the summary tables of adverse events.

Any AE occurring within the defined 30 day follow-up period after discontinuation of investigational product will be included in the AE summaries. AEs occurring after the 90 day follow-up period after discontinuation of investigational product will be listed separately, but not included in the summaries. Hematology, clinical chemistry, vital signs, ECG data, urinalysis, demographic data, medical histories and concomitant medications will be listed individually by subject and suitably summarized. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used. Details of any deaths will be listed for all subjects. Any qualitative assessments will be summarized for all subjects using the number of subjects with results of negative, trace or positive. Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

Tumor response
Tumor response data will be summarized for dosed subjects with measurable disease at baseline.

Objective response rate, disease control rate and PFS will be summarized in the expansion phase arm.

Tumor response will be analyzed using RECIST 1.1 criteria (Appendix B) and the immune response criteria.[29] Confirmation of immune response will be done at the discretion of the investigator.

In this classification, the overall response is determined as follows:

- Immune response CR (irCR) is a complete disappearance of all lesions (whether measurable or not, and no new lesions) with confirmation by a repeat, consecutive assessment no less than 4 weeks from the first documentation.
- Immune response PR (irPR) is a decrease in tumor burden of greater than or equal to 50% relative to baseline. This must be confirmed by a consecutive assessment at least 4 weeks after the first documentation.
- Immune response SD (irSD) is classified as those who do not meet criteria for irCR or irPR and who do not have irPD
- Immune response PD (irPD) is an increase in tumor burden of greater than or equal to 25%relative to the minimum recorded tumor burden which must be confirmed by a repeat, consecutive assessment no less than 4 weeks from the first documentation.

10. Data Recording

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

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

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

10.2 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.3 Record Retention

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

patient consent forms).

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

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.4 Obligations of Investigators

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

11. Ethical and Legal Aspects

11.1 Ethical and Legal 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 investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Janssen Scientific Affairs, LLC. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Janssen approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and, if appropriate, the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

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

The Principal Investigator will be responsible for assuring that all the required data will be collected and properly documented.

11.2 **Subject Information and Consent**

Each subject/legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject/legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject/legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

1. If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of Janssen/Merck, and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.
3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects/legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written informed consent form. The investigator will inform the subject/legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval/favorable opinion in advance of use.

11.3 **Confidentiality**

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.4 **Flow cytometry**

The isolated peripheral blood mononuclear cells before, during and after treatment will be analyzed to measure the frequency of effector T cells and regulatory T cells (Treg)s using flow cytometry. Eight color flow cytometry analysis will be performed on the isolated mononuclear cells using the following antibodies: florescence conjugated anti-CD3, anti-CD4, anti-CD8, anti-CD25, anti-CD127, anti-Foxp3, anti-granzyme B and anti-perforin (BD Bioscience or eBioscience). For extracellular staining, cells will be incubated for 30 minutes at 4°C with optimal dilution of each antibody. Intracellular staining for Foxp3, granzyme B and perforin will be preceded by fixation and permeabilization with intracellular staining kit (eBioscience). Flow cytometry will be performed on a FACS LSRFortessa (BD) and analyzed using CellQuest software (BD). The results of flowcytometry pre and post treatment will be correlated with the clinical efficacy to identify possible mechanisms of tumor response

[redacted]

13. Appendix

APPENDIX A: CYP3A Inhibitors

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 5.2 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Aprepitant	St. John's Wort
Erythromycin	Troglitazone
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

APPENDIX B: RECIST Criteria for Measuring Tumor Response Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer et al., 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ibrutinib or pembrolizumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, MRI or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might be considered measurable if the lesion has increased in size since the radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in

which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.,* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Response Criteria Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Principal Investigator.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first

14. Appendix C: Janssen Safety Language

As the sponsor of the Study, Moffitt Cancer Center shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. Safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

Moffitt Cancer Center will provide safety information to Janssen Scientific Affairs, LLC on adverse events, special situations including pregnancies and product quality complaints as

defined below:

1. **Management of Safety Data**

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this section will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product is: Ibrutinib (Imbruvica)

2. **Definitions**

2.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non- investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

2.2. Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC. is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Major Hemorrhage
  Major hemorrhage is defined as any hemorrhagic event that is Grade 3 or greater in severity or that results in 1 of the following: intraocular bleeding causing loss of vision, the need for a transfusion of 2 or more units of red cells or an equivalent amount of whole blood, hospitalization, or prolongation of hospitalization.
- Intracranial Hemorrhage
  Any intracranial hemorrhage adverse event, including subdural hematoma/hemorrhage, epidural hematoma/hemorrhage and intracerebral hemorrhage, of any grade severity, will be captured as an event of special interest.
- Other Malignancies
  In addition to all routine AE reporting, all new malignant tumors, including solid tumors, skin malignancies and hematologic malignancies, are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

2.3. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

2.4. Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

2.5. Serious Adverse Event (SAE)

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

2.5.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

2.5.2. Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

3. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

http://www.imbruvica.com/hcp/?utm_source=google&utm_medium=cpc&utm_campaign=Imbruvica&utm_term=imbruvica&utm_content=ibrutinib-+Exact|mkwid|ssjPpM0Gh_dc|pcrid|39412243694

4. Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC **within 24 hours of becoming aware of the event.**

Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC within 24 hours of their knowledge of the event using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must promptly discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in

partners of male subjects exposed to a Janssen medicinal product will be reported **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

5. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. Moffitt Cancer Center shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

6. Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up in accordance with clinical practice.

6.1. SAEs and Special Reporting Situations

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Moffitt Cancer Center will transmit all SAEs and special situations following exposure to a Janssen product under study in a form provided by Janssen Scientific Affairs, LLC in accordance with Section 10 ,Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported within **24 hours becoming aware**, to Janssen Scientific Affairs, LLC using the Janssen Scientific Affairs,

LLC Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE or special situation is required.

- The principal investigator is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to Janssen Scientific Affairs, LLC using a transmission method in Section 10 within **24 hours of such report or correspondence being sent to applicable health authorities.**

6.2. Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

6.3. PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC by Moffitt Cancer Center **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, Moffitt Cancer Center must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

7. Reporting Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Non-Janssen Medicinal Products

For SAEs, special reporting situations and PQCs following exposure to a non-Janssen medicinal product under study, Moffitt Cancer Center should notify the appropriate regulatory/competent authority or the manufacturer of that medicinal product (in the absence of appropriate local legislation) as soon as possible.

8. Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

15. References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer* 2015; **136**(5): E359-E86.
2. Van Cutsem E, Nordlinger B, Cervantes A. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Annals of Oncology* 2010; **21**(suppl 5): v93-v7.
3. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**(9863): 303-12.
4. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2015; **16**(6): 619-29.
5. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. *New Engl J Med* 2015; **372**(20): 1909-19.
6. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nature Reviews Immunology* 2008; **8**(6): 467-77.
7. Kroemer G, Galluzzi L, Zitvogel L, Fridman WH. Colorectal cancer: the first neoplasia found to be under immunosurveillance and the last one to respond to immunotherapy? *Oncoimmunology* 2015; **4**(7): e1058597.
8. Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti–programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. *Journal of Clinical Oncology* 2010; **28**(19): 3167-75.
9. Xiang B, Snook AE, Magee MS, Waldman SA. Colorectal cancer immunotherapy. *Discovery medicine* 2013; **15**(84): 301.
10. Grabinski N, Ewald F. Ibrutinib (ImbruvicaTM) potently inhibits ErbB receptor phosphorylation and cell viability of ErbB2-positive breast cancer cells. *Investigational new drugs* 2014; **32**(6): 1096-104.
11. Gao W, Wang M, Wang L, et al. Selective Antitumor Activity of Ibrutinib in EGFR-Mutant Non–Small Cell Lung Cancer Cells. *Journal of the National Cancer Institute* 2014; **106**(9): dju204.
12. Berglöf A, Hamasy A, Meinke S, et al. Targets for Ibrutinib Beyond B Cell Malignancies. *Scandinavian journal of immunology* 2015; **82**(3): 208-17.
13. Chen J, Chang BY, Elias L. Inhibitory effects of the BTK inhibitor, ibrutinib, on Her2 amplified breast cancer growth, cell cycle progression and clonogenicity. *Cancer Research* 2014; **74**(19 Supplement): 4564-.
14. Massó-Vallés D, Jauset T, Serrano E, et al. Ibrutinib exerts potent antifibrotic activity in a mouse model of pancreatic adenocarcinoma. *Cancer Research* 2015; **75**(15 Supplement): 396-.
15. Sagiv-Barfi I, Kohrt H, Czerwinski D, Ng P, Chang B, Levy R. Combining Ibrutinib with immune checkpoint blockade to induce therapeutic antitumor immune response in solid tumors. *Cancer Research* 2015; **75**(15 Supplement): 251-.
16. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *New England Journal of Medicine* 2014; **371**(3): 213-23.
17. O'Brien S, Furman RR, Coutre SE, et al. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label,

multicentre, phase 1b/2 trial. *The lancet oncology* 2014; **15**(1): 48-58.
18. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *New England Journal of Medicine* 2013; **369**(6): 507-16.
19. Tripsas CK, Yang G, Cao Y, et al. A prospective multicenter study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenstrom's macroglobulinemia. *Blood* 2013; **122**(21): 251-.
20. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer* 2012; **12**(4): 252-64.
21. Topalian SL, Drake CG, Pardoll DM. Targeting the PD-1/B7-H1 (PD-L1) pathway to activate anti-tumor immunity. *Current opinion in immunology* 2012; **24**(2): 207-12.
22. Le DT, Uram JN, Wang H, et al. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *The New England journal of medicine* 2015; **372**(26): 2509-20.
23. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *New England Journal of Medicine* 2015; **372**(26): 2521-32.
24. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. *New England Journal of Medicine* 2015; **372**(21): 2018-28.
25. Sagiv-Barfi I, Kohrt HE, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. *Proceedings of the National Academy of Sciences* 2015; **112**(9): E966-E72.
26. Castle JC, Loewer M, Boegel S, et al. Immunomic, genomic and transcriptomic characterization of CT26 colorectal carcinoma. *BMC genomics* 2014; **15**(1): 190.
27. Ng P, Lu D, Chang B. Ibrutinib enhances the anti-tumor efficacy of CTLA-4 blockade in lymphoma and colon cancer models. *Cancer Research* 2015; **75**(15 Supplement): 259-.
28. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**(1): 1-10.
29. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clinical Cancer Research* 2009; **15**(23): 7412-20.