PROTOCOL

TITLE:	A Multi-Center Open-Label Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with MEDI4736, in Subjects with Relapsed or Refractory Lymphomas
PROTOCOL NUMBER:	**PCYC-1136-CA**
STUDY DRUG(S):	Ibrutinib and MEDI4736
IND NUMBER:	102,688
SPONSOR MEDICAL MONITOR:	Alvina Chu, MD Pharmacyclics, Inc. Phone: +1 (408) 215-3027 Fax: +1 (408) 215-3684 Email: achu@pcyc.com
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DATE FINAL:	29 December 2014
AMENDMENT 1 FINAL:	20 February 2015

PROTOCOL APPROVAL PAGE

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Study Number: **PCYC-1136-CA**

Amendment 1 Date: 20 February 2015

I have carefully read Protocol PCYC-1136-CA, Amendment 1 entitled "A Multi-Center Open-Label Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with MEDI4736, in Subjects with Relapsed or Refractory Lymphomas". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics, Inc requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics, Inc. representative is authorized to sign the protocol and any amendments:

Alvina Chu, MD 23 Feb 2015

Medical Monitor's Signature Date
Alvina Chu, MD
Clinical Development, Pharmacyclics, Inc.

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SYNOPSIS

Study Title:	A Multi-Center Open-Label Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib, in Combination with MEDI4736, in Subjects with Relapsed or Refractory Lymphomas
Protocol Number:	PCYC-1136-CA
Study Phase:	1b/2
Study Duration:	Estimated to be approximately 3 years
Number of Subjects:	Approximately 109 subjects will be enrolled throughout the study (up to 36 subjects in Phase 1b and approximately 73 subjects in Phase 2)
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. MEDI4736 will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration.
Objectives:	**<u>Phase 1b:</u>** **Primary Objectives:** • To determine the recommended Phase 2 dose (RP2D) of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas • To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas **Secondary Objectives**: • To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the overall response rate (ORR) • To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the duration of response (DOR) • To determine the pharmacokinetics (PK) and pharmacodynamics of both ibrutinib and MEDI4736 in subjects with relapsed or refractory lymphomas **<u>Phase 2:</u>** **Primary Objective:** • To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the ORR **Secondary Objectives:** • To determine the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the DOR, progression-free survival (PFS), and overall survival (OS)

	• To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed and refractory lymphomas • To determine the PK and pharmacodynamics of both ibrutinib and MEDI4736 in subjects with relapsed or refractory lymphomas **Exploratory Objectives:** • To evaluate immune cell subsets after treatment with ibrutinib in combination with MEDI4736 • To evaluate non-BTK related pharmacodynamics (ie, interleukin-2-inducible T-cell kinase [ITK]) after treatment with ibrutinib in combination with MEDI4736 • To evaluate chemokine/cytokine levels after treatment with ibrutinib in combination with MEDI4736 • To identify genes and proteins associated with sensitivity or resistance to ibrutinib and/or MEDI4736 combination (ie, PD-1 ligand [PD-L1]) • To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the rate and duration of minimal residual disease (MRD) negativity
Study Design:	This is a Phase 1b/2, open-label multi-center study to assess the safety and efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas. A 6+3 de-escalation design will be employed in Phase 1b to assess doses of ibrutinib in combination with MEDI4736 to determine the RP2D for this study. **Phase 1b**: In the safety portion of the study, a starting dose of 560 mg of ibrutinib and 10 mg/kg of MEDI4736 will be explored in Cohort 1 and will follow a 6+3 dose de-escalation design including a sentinel subject with at least a 3-day observation period in each Phase 1b dosing cohort prior to dosing additional subjects to monitor for any unexpected acute or overlapping toxicities. Subjects with one of the following two tumor types will be eligible for enrollment in Phase 1b: • Follicular lymphoma (FL) (grade 1, 2, or 3A) • Diffuse large B cell lymphoma (DLBCL) In cohort 1, ibrutinib will be administered orally (PO) daily in 6 subjects at a dose of 560 mg in combination with MEDI4736 at a dose of 10 mg/kg intravenously (IV) every 2 weeks in 28-day cycles for 12 months or until unacceptable toxicity or disease progression occurs. As a lead-in to the first cycle, ibrutinib will be given for 7 days prior to starting MEDI4736 in order to obtain single agent PK and biomarker samples that can be compared to combination therapy. If the subject incidence of dose-limiting toxicities (DLTs) from Day 1 of Cycle 1 of combination therapy to the laboratory evaluations on Day 1 of Cycle 2 is <33.3% (ie, ≤1 of 6 or ≤2 of 9 subjects with a DLT), this dose

	level will be considered safe to proceed to Phase 2, and will be defined as the RP2D. If 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6–9 subjects experience a DLT, dose de-escalation will occur. A similar 6+3 cohort design will be utilized in the de-escalation cohorts. De-escalation cohorts -1A and -1B will be opened simultaneously to determine which dosing schedule is most appropriate for the phase 2 portion of the study (for cohort definitions, see synopsis section: Study Treatment). Determination will be based on the safety profile of the 2 treatment regimens. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter. The Phase 1b DLT observation period will occur from Day 1 of Cycle 1 of ibrutinib in combination with MEDI4736 treatment until the laboratory evaluations on Day 1 of Cycle 2 which will occur before the MEDI4736 infusion on Day 1 of Cycle 2. A DLT is an AE at least possibly related to study drug(s) defined as: Any Grade 3 or higher non-hematologic AE (with additional clarifications below) • Grade 3 or higher nausea, vomiting, or diarrhea (non-colitis-related) that is uncontrolled by maximal supportive care and persists for >7 days would be considered a DLT • Grade 3 fatigue that persists for >7 days would be considered a DLT • Any Grade 3 immune related adverse event (irAE) that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids, or does not downgrade to Grade ≤1 or baseline within 14 days would be considered a DLT • Any Grade ≥2 pneumonitis that does not resolve to Grade ≤1 within 3 days of the initiation of maximal supportive care would be considered a DLT. • The DLT definition excludes the following conditions: o Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic o Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc) o Vitiligo or alopecia of any AE grade would not be considered a DLT 2) Clinically relevant hematologic AE such as: • Grade 3 or 4 neutropenia (ANC<1,000/ mm^3) lasting >7 days • Febrile neutropenia (Grade 3 or 4 neutropenia with fever ≥38.3ºC) • Grade 3 or 4 thrombocytopenia (<25,000/ mm^3) lasting >7 days or

	requiring transfusion or associated with Grade ≥2 bleeding • Any other Grade 4 hematologic AE, except lymphopenia During the Phase 1b DLT observation period of ibrutinib in combination with MEDI4736, subjects will be replaced for any of the following reasons: • Missed ≥5 consecutive doses of ibrutinib or missed 7 total doses (not due to DLT) • Missed dose of MEDI4736 or received the MEDI4736 dose outside of the protocol-allowed window (±2 days) (not due to DLT) • Study drug discontinuation for any reason other than DLT After the RP2D of ibrutinib in combination with MEDI4736 is defined, enrollment in Phase 2 will commence. **Phase 2:** Two tumor types will be enrolled in separate cohorts as part of this protocol: • Follicular lymphoma (FL) (grade 1, 2, or 3A) • Diffuse large B cell lymphoma (DLBCL) **For FL: n = 39** The FL cohort will enroll 39 response-evaluable subjects. An interim analysis will be performed after 19 subjects are evaluable for tumor response after completing at least 2 response assessments. If only 6 or fewer responders (≤6/19) are observed, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment of responders) or tumor measurements (showing clinically relevant tumor reductions, ie, 40%, that fit the criteria for SD) may support continued enrollment (see Section 12.11). **For DLBCL: n = 34** Subjects with germinal center B-cell (GCB) and non-GCB subtypes will be enrolled at a 1:1 ratio approximately. The DLBCL cohort will enroll 34 response-evaluable subjects. An interim analysis will be performed after 9 subjects are evaluable for tumor response after completing at least 2 response assessments. If only 1 or fewer responder (≤1/9) is observed, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment of responders) or tumor measurements (showing clinically relevant tumor reductions, ie, 40%, that fit the criteria for SD) may support continued enrollment (see Section 12.11). In the DLBCL cohort, additional prospectively identified non-GCB subjects may be enrolled if a 22% ORR (2/9) is not achieved at the interim analysis in the unselected DLBCL population so that at least a total of 16 subjects with the non-GCB subtype are evaluated. Note: The Phase 2 subjects include all of those subjects treated at R2PD in Phase 1b but with tumor type as defined for Phase 2.

	During the Phase 2 portion of the study, if a subject discontinues study drug prior to the first tumor response assessment for reasons other than progressive disease, the subject may be replaced. The primary analysis will occur at least 12 months after the last FL subject is enrolled and at least 9 months after the last DLBCL subject is enrolled. Dosing of ibrutinib in combination with MEDI4736 will continue for a total of 12 cycles of therapy if the subject is deriving clinical benefit (CR, PR, or SD) and the subject is not experiencing unacceptable toxicity. After 12 cycles, dosing of ibrutinib alone will continue as long as clinical benefit is seen without safety concerns or disease progression. Response evaluations will occur on Day 1 of Cycle 3 and then after every 3rd cycle through the 1st year and after every 6th cycle thereafter. Assessment will follow the Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014). In order to accommodate the potential for immune flare (pseudoprogression), treatment with MEDI4736 and ibrutinib may continue between the initial assessment of suspected progression and confirmation of progression. Subjects with presumed progressive disease (PD) who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive MEDI4736 and ibrutinib as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion (see Section 12.11). In the absence of clinically significant deterioration, a CT scan or biopsy may be performed at least 4 weeks later to confirm PD. If PD is confirmed at the later time point, PD should be assigned to the prior time point at which PD criteria were also met. MEDI4736 and ibrutinib should be discontinued if there is confirmed PD per Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014) or other clinical data suggest clear evidence of progression. Subjects are required to undergo a pre-treatment tumor biopsy for all phases of this study; a post-progression biopsy is recommended but will be optional.
Population:	Subjects with relapsed or refractory: • Follicular lymphoma (FL) (grade 1, 2, or 3A) • Diffuse large B cell lymphoma (DLBCL)
Centers:	Multi-center, United States (US) only
Inclusion Criteria:	1. Men and women ≥ 18 years of age 2. Pathologically confirmed: A. Phase 1b: diffuse large B-cell lymphoma or follicular lymphoma (grade 1, 2, or 3A) according to World Health Organization (WHO) criteria B. Phase 2: diffuse large B-cell lymphoma or follicular lymphoma (grade 1, 2, or 3A) according to WHO criteria without clinical or pathological evidence of transformation 3. Provision of a fresh tumor biopsy or an available archival tumor sample processed as formalin-fixed, paraffin-embedded (FFPE) taken within 3 months of screening, and after the most recent treatment

	(Note: Earlier archived tumor tissue from all enrolled subjects will also be requested.) 4. Relapsed or refractory disease: A. DLBCL 1) Relapsed or refractory disease, defined as: a) Recurrence of disease after a complete response (CR) OR b) Partial response (PR), stable disease (SD) or progressive disease (PD) at completion of the treatment regimen preceding entry to the study (residual disease) 2) Subjects who have not already had a stem cell transplant must not be considered a candidate for high dose chemotherapy with stem cell transplant (HDT/SCT) and must meet at least one of the following criteria: a) Age ≥70 years b) Diffuse lung capacity for carbon monoxide <50% by pulmonary function test c) Left ventricular ejection fraction <50% by multiple gated acquisition /echocardiogram d) Other organ dysfunction or co-morbidities precluding the use of HDT/SCT on the basis of unacceptable risk of treatment-related morbidity e) Failure to achieve PR or CR with salvage therapy f) Subject refusal of HDT/SCT B. FL 1) Previously received at least one appropriate chemoimmunotherapy regimen and have relapsed or refractory disease 5. Measurable disease: One or more measurable disease sites on CT scan (>1.5 cm in longest dimension) is required. Lesions in anatomical locations (such as extremities or soft tissue lesions) that are not well visualized by CT may be measured by MRI instead. 6. Adequate hematologic function independent of transfusion support for at least 7 days prior to screening and independent of growth factor support for at least 14 days prior to screening, defined as: • Absolute neutrophil count >1500 cells/mm^3 (1.50 x 10^9/L) • Platelet count >50,000 cells/mm^3 (50 x 10^9/L) unless there is documented bone marrow involvement • Hemoglobin >8.0 g/dL 7. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) • Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome such that bilirubin ≤3.0 x ULN or is of non-hepatic

	origin) • Estimated Creatinine Clearance ≥40 mL/min (Cockcroft-Gault) 8. Prothrombin time (PT) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN 9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 10. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry. 11. Male subjects who are not sterilized and who are sexually active with a female partner of childbearing potential and female subjects of childbearing potential who are sexually active with a nonsterilized male partner must agree to use 2 highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, or intrauterine devices [IUDs]) during the period of therapy and for 3 months after the last dose of study drug (see Appendix 7). 12. Male subjects must agree to not donate sperm, and female subjects must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during or for 3 months after the last dose of either study drug.
Exclusion Criteria:	1. Anti-tumor therapy (chemotherapy, antibody therapy, immunotherapy, biologic-based therapy, or investigational agent) within 14 days of study Day 1 (or 6 weeks for nitrosureas or mitomycin C); Enrollment of subjects that have received molecularly-targeted small molecule inhibitors less than 28 days prior to study Day 1 will be permitted if more than 14 days and at least 5 drug half-lives have passed prior to receiving the first dose of ibrutinib. 2. Prior therapy with ibrutinib or other BTK inhibitor and/or anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody 3. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03) grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of stable neuropathy, vitiligo, alopecia, or other irreversible toxicity not reasonably expected to be exacerbated by study treatment (eg, hearing loss) 4. Treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 4) 5. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug (Note: Subjects, if enrolled, should not receive live vaccines during the study and until 30 days after the last dose of study drug) 6. Current or prior use of immunosuppressive medication within 14 days

	before the first dose of MEDI4736. The following are exceptions to this criterion: • Intranasal, inhaled, topical corticosteroids, or local corticosteroid injections (eg, intra-articular injection) • Systemic corticosteroids at doses not to exceed 10 mg/day of prednisone or its equivalent • Corticosteroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication) 7. History of allogeneic organ transplant or <100 days after autologous transplant 8. Primary central nervous system (CNS) lymphoma or evidence of CNS involvement by lymphoma 9. Any uncontrolled active systemic infection, or recent infection requiring intravenous antibiotic treatment that was completed ≤14 days before the first dose of study drug 10. Known history of previous clinical diagnosis of active tuberculosis 11. Known bleeding disorders (eg, von Willebrand's disease or hemophilia) 12. History of stroke or intracranial hemorrhage within 6 months prior to enrollment 13. Major surgery within 4 weeks of first dose of study drug 14. Concomitant use of warfarin or other Vitamin K antagonists 15. History of primary immunodeficiency 16. Known history of human immunodeficiency virus (HIV) or current chronic/active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) • Subjects with chronic or active hepatitis B as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction (PCR) may be performed and must be negative for enrollment. 17. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification (see Appendix 6); or a history of myocardial infarction, uncontrolled hypertension or cardiac arrhythmia, unstable angina, or acute coronary syndrome within 6 months prior to enrollment 18. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia formula 19. Unable to swallow capsules or malabsorption syndrome, disease or condition significantly affecting gastrointestinal function, or resection of the stomach or small bowel, or partial or complete bowel obstruction 20. Lactating women, men planning to father a child, or women planning pregnancy while taking study drug or within 3 months after the last dose of study drug

	21. Known allergy or hypersensitivity to ibrutinib or MEDI4736 or any excipient 22. Active or prior documented autoimmune or inflammatory disorders including but not limited to inflammatory bowel disease (eg, colitis, Crohn's disease), diverticulitis with the exception of a prior resolved episode or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea, type I diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, Wegener's granulomatosis (granulomatosis with polyangiitis), myasthenia gravis, Graves' disease, rheumatoid arthritis, pneumonitis, interstitial lung disease, hypophysitis, or uveitis within the past 3 years prior to the start of treatment. The following are exceptions to this criterion: • Subjects with vitiligo or alopecia • Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment 23. History of other malignancies, except • Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by the treating physician • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without evidence of disease 24. Unwilling or unable to participate in all required study evaluations and procedures 25. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk, eg, psychiatric illness/social situations that would limit compliance with study requirement or compromise the ability of the subject to give written informed consent 26. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) 27. Concurrent enrollment in another clinical study, unless in a follow-up period or in an observational study
Study Treatment:	One cycle of treatment is 28 days in duration and consists of daily administration of ibrutinib PO with MEDI4736 IV every 2 weeks. As a lead-in to the first cycle, ibrutinib will be given for 7 days prior to starting MEDI4736 in order to obtain single agent PK and biomarker samples that can be compared to the PK when ibrutinib is administered in combination with MEDI4736. Dosing of ibrutinib in combination with MEDI4736 will continue for a total of 12 cycles of therapy if the subject is deriving clinical benefit (CR, PR, or SD) and the subject is not experiencing unacceptable toxicity. Re-treatment with MEDI4736 will not be allowed following

	completion of 12 cycles of treatment, regardless of any dose delays, missed doses, or following permanent discontinuation for any reason. After 12 cycles, dosing of ibrutinib alone will continue as long as clinical benefit is seen without safety concerns or disease progression. **Phase 1b (including de-escalation cohorts):** Cohort 1 ibrutinib 560 mg PO qd, MEDI4736 10 mg/kg IV q2 weeks Cohort -1A ibrutinib 420 mg PO qd, MEDI4736 10 mg/kg IV q2 weeks Cohort -1B ibrutinib 560 mg PO qd, MEDI4736 3 mg/kg IV q2 weeks Cohort -2 ibrutinib 420 mg PO qd, MEDI4736 3 mg/kg IV q2 weeks **Phase 2:** RP2D established in Phase 1b (420 mg or 560 mg PO ibrutinib daily and 3 mg/kg or 10 mg/kg IV MEDI4736 q2 weeks) given continuously in 28-day cycles in the following two cohorts: • Follicular lymphoma (FL) (grade 1, 2, or 3A) • Diffuse large B cell lymphoma (DLBCL)
Safety Monitoring:	AEs and serious adverse events (SAEs) will be reviewed by the Sponsor on an ongoing basis to identify safety concerns. A Dose Level Review Committee will evaluate the safety data from the 1b portion of the trial. Members of this committee will include participating investigators or designee as well as the Sponsor (invitees include: the Medical Monitor or designee, the clinical lead, a Drug Safety representative and a Biostatistician) (see Section 12.11).
Statistical Methods and Data Analysis:	Tumor response assessment will follow the Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014). **Phase 1b:** Phase 1b is based on a 6+3 de-escalation design described in the Study Design Section to determine the RP2D. A primary objective is to evaluate safety and tolerability of ibrutinib in combination with MEDI4736. AEs including DLTs, laboratory values, and dosing data will be listed and summarized by tumor type and dose cohort. Secondary objectives are to evaluate efficacy and PK and pharmacodynamics in subjects receiving the combination regimen. ORR and DOR will be calculated and summarized by tumor type and dose cohort descriptively. PK and pharmacodynamics (ie, BTK) data will be evaluated by tumor type and dose cohort. **Phase 2:** Phase 2 will use the RP2D ascertained in Phase 1b to treat approximately 73 subjects (39 FL and 34 DLBCL subjects). For Phase 2 the following analyses will be undertaken: **Primary Efficacy Endpoint:**

	The primary efficacy endpoint is the ORR in each of the two cohorts. The observed ORR along with its 95% confidence interval will be calculated for each tumor type. **Secondary Efficacy Endpoints:** • DOR will be calculated and summarized by descriptive statistics for responders by tumor type. The Kaplan-Meier estimate will be provided for DOR if a sufficient number of responders are observed. • PFS and OS will be evaluated by tumor type with Kaplan-Meier estimates. • PK and pharmacodynamics profiles will also be evaluated by tumor type. **Exploratory Efficacy Analysis:** The exploratory efficacy variables will be summarized descriptively and include the following: • Immune cell subsets • Non-BTK related pharmacodynamics (ie, ITK) • Chemokine/cytokine levels • Genes and proteins associated with sensitivity or resistance to ibrutinib and/or MEDI4736 (ie, PD-L1) • Rate and duration of MRD negativity For each cohort, a subgroup analysis will be conducted to calculate ORR and its 95% confidence interval based on PD-1 ligand expression (positive versus negative). For the DLBCL cohort, a subgroup analysis will also be conducted based on subjects with GCB and non-GCB subtype, respectively. **Safety Analysis:** AEs, SAEs, laboratory data, vital signs, other relevant safety data, and dosing data will be listed and summarized by cohort.
Sample Size Determination:	**Phase 1b:** 6-36 subjects for DLT assessment (6-9 subjects in up to 4 dose de-escalation cohorts, regardless of tumor type) **Phase 2:** Approximately 73 response-evaluable subjects (including those subjects treated at the RP2D in Phase 1b but with tumor type as defined for Phase 2). **For FL**: A maximum of 39 response-evaluable subjects (including those subjects treated at the RP2D in Phase 1b and with tumor type of FL) will be enrolled. An interim analysis will be performed after 19 subjects are evaluable for tumor response after completing at least 2 response assessments. If only 6 or fewer responders (≤6/19) are observed, the Sponsor may consider discontinuation of this cohort (see Section 12.11).

	The null hypothesis that the true ORR is 30% will be tested against a one-sided alternative that the ORR is 50%. The null hypothesis will be rejected if 17 or more responses are observed in the 39 subjects. This design yields a 1-sided type I error rate of 0.05 and power of 80% when the true ORR is 50%. This statistical design including number of subjects and number of responders follows the statistical framework of Simon's minimax two-stage design (Simon, 1989). Enrollment will continue while the interim analysis is performed. **For DLBCL:** A maximum of 34 response-evaluable subjects with GCB and non-GCB (inclusive of subjects treated at the RP2D in Phase 1b in the unselected DLBCL population) will be enrolled at a 1:1 ratio approximately. An interim analysis will be performed after 9 subjects are evaluable for tumor response after completing at least 2 response assessments. If only 1 or fewer responder (≤1/9) is observed, the Sponsor may consider discontinuation of this cohort (see Section 12.11). The null hypothesis that the true ORR is 15% will be tested against a one-sided alternative that the ORR is 35%. The null hypothesis will be rejected if 9 or more responses are observed in the 34 subjects. This design yields a 1-sided type I error rate of 0.05 and power of 80% when the true ORR is 35%. This statistical design including number of subjects and number of responders follows the statistical framework of Simon's optimal two-stage design (Simon 1989). Enrollment will continue while the interim analysis is performed.

ABBREVIATIONS

ABC	activated B cell
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-14}	area under the curve from zero to 14 days
AUC_{0-24}	area under the curve from zero to 24 hours
BCR	B-cell receptor
BMI	body mass index
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CEOP	cyclophosphamide, etoposide, vincristine, prednisone
CEPP	cyclophosphamide, etoposide, prednisone, procarbazine
CHO	Chinese hamster ovary
CI	confidence interval
CL	systemic clearance
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CYP	cytochrome P450
DA-EPOCH	dose-adjusted cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone
DLBCL	diffuse large B-cell lymphoma
DLRC	Dose Level Review Committee
DLT	dose-limiting toxicity
DOR	duration of response
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group performance status
ECG	Electrocardiogram
FCR	fludarabine/cyclophosphamide/rituximab
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FL	follicular lymphoma
G-CSF	granulocyte-colony stimulating factor
GCB	germinal center B cell
GCP	Good Clinical Practice
GDP	gemcitabine, dexamethasone, cisplatin
GemOx	gemcitabine, oxaliplatin
GGT	gamma-glutamyltransferase
GLP	good laboratory practices

HBV	hepatitis B virus
HCV	hepatitis C virus
HDT/SCT	high dose chemotherapy with stem cell transplant
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin
ILD	interstitial lung disease
INR	International normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
ITK	interleukin-2-inducible T-cell kinase
JC	John Cunningham
K_m	Michaelis constant
LD	longest diameter
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimum residual disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NHL	non-Hodgkin lymphoma
NOAEL	no-observed-adverse-effect level
NONMEM	nonlinear mixed-effects modeling
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	Overall survival
PBMC	peripheral blood mononuclear cells
PBML	primary mediastinal
PCR	Polymerase Chain Reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	per os (oral)
PR	partial response
aPTT	activated partial thromboplastin time
PT	prothrombin time

QTc	QT interval corrected for heart rate
Q2W	every 2 weeks
R-CHOP	rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone
R-CVP	rituximab, cyclophosphamide, vincristine, prednisone
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SJS	Stevens-Johnson Syndrome
sPD-L1	soluble PD-L1
$t_{1/2}$	half-life
T_h	helper T cell
T_{max}	time to maximum plasma concentration
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. BACKGROUND

1.1 Diffuse Large B-cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common of the non-Hodgkin lymphomas (NHLs) in the United States, with an annual incidence that has been rising gradually since the 1990s (Fisher 2004). The estimated 2010 prevalence of NHL in the US was approximately 509,000 individuals, with over 200,000 of these cases in individuals over the age of 70 years (SEER 2010). It is estimated that 30–40% of NHL cases are of the DLBCL category (Hans 2004). According to the current Surveillance, Epidemiology, and End Results (SEER) data, the median age at diagnosis is 67 years (SEER 2010). A very aggressive malignancy in its untreated natural history, DLBCL is a potentially curable disease, with a significant proportion of patients cured with modern chemoimmunotherapy. Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor (Gisselbrecht 2010) and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies.

DLBCL gene expression profiling reveals 3 molecular subtypes: activated B cell (ABC), germinal center B cell (GCB) and primary mediastinal (PMBL). The ABC subtype accounts for ~30% of cases of DLBCL and has an inferior prognosis. Chronic active B-cell receptor (BCR) signaling is a pathogenic mechanism in ABC DLBCL and this chronic activation engages the classic nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. In contrast, GCB DLBCL pathogenesis is independent of the NF-κB pathway (Lenz 2010). This difference in the molecular mechanism of pathogenesis may explain why the ABC subtype is less sensitive to chemotherapy and remains less curable than the GCB subtype. Thus, new strategies for the ABC subtype are needed.

Treatment for relapsed and refractory DLBCL remains challenging. Following initial therapy, the approach of re-induction chemotherapy followed by high-dose chemotherapy with stem cell transplant (HDT/SCT) for responding patients remains the current standard of care. For patients that are not eligible for stem cell therapy, per National Comprehensive Cancer Network (NCCN) guidelines, a variety of therapies are recommended for second line treatment. These include DA-EPOCH (dose-adjusted cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) +/- rituximab (Jermann 2004; Wilson 2008), CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) +/- rituximab (Chao 1990), CEOP (cyclophosphamide, etoposide, vincristine, prednisone) +/- rituximab (Bartlett 2001; Moccia 2009), GDP (gemcitabine, dexamethasone, cisplatin) +/- rituximab (Crump 2004), GemOx (gemcitabine, oxaliplatin) +/- rituximab (Lopez 2008; Corazzelli 2009; El Gnaoui 2007), Bendamustine +/- rituximab (Ohmachi 2013; Weidmann 2002; Rigacci 2012), Lenalidomide +/- rituximab (Wiernik 2008; Witzig 2011) and rituximab single-agent therapy (Robach 2002). These therapeutic options are largely chemotherapy-based and offer a poor prognosis in non-GCB subjects including the ABC subtype. Recurrent or resistant DLBCL in patients ineligible for transplantation is particularly difficult to treat and is associated with a markedly reduced survival (Thieblemont 2007;

Jabbour 2004). Treatment options are also limited for those who have failed stem cell transplant or salvage chemotherapy-based strategies (Martelli 2013).

Treatment of patients with relapsed or refractory DLBCL with chemotherapy-free regimens such as ibrutinib and MEDI4736 may be an attractive treatment option if found to be well tolerated and have significant anti-tumor activity. Alternative treatment options with a favorable safety profile for recurrent or relapsed disease in a heavily pretreated patient population are still needed.

1.2 Follicular Lymphoma

Follicular lymphoma (FL) is the second most common NHL accounting for approximately 22% of cases (NHL Classification Project 1997). The overall incidence of FL is 3.18 new cases per 100,000 persons each year in the United States (US) (Morton 2006). FL is characterized by an indolent clinical course, typical morphology, and the presence of a chromosomal translocation, t(14;18)(q32;q21) or variant in 85% of patients (Relander 2010). The neoplastic lymphocytes in FL express pan-B markers CD19, CD20, CD22, and CD79a; as well as antigens of the germinal center (including CD10 and Bcl-6). Histologically, the follicular form of NHL is composed mainly of centrocytes with an admixture of centroblasts. Grading is based on the number of large transformed cells in 10 malignant follicles viewed at high power (Martinez 2007). FL is generally subdivided into 3 grades (NHL Classification Project 2007). However, Grade 3 is often further divided into 2 subgroups, 3a and 3b; with 3b considered more aggressive (Hans 2003). Importantly, primary FL cells have been found to maintain enhanced signaling from the BCR compared to normal B cells (Irish 2006). Treatment often depends on the stage of the disease, symptoms, patient age, and comorbidities.

Alkylating agents such as cyclophosphamide or bendamustine, in combination with rituximab, constitute the mainstay of combination therapy. The most commonly used alkylator-based regimens include BR (bendamustine and rituximab), R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone), or R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone) (Lymphoma Research Foundation, 2011). Response rates in excess of 85% are observed with many different combinations in the first-line setting (Peterson 2003, Hiddeman 2005, Czuczman 2005, Rummel 2005); however, most patients treated will eventually relapse, and subsequent responses become increasingly shorter in duration and less frequent. Patients who become resistant to chemoimmunotherapy, clinically defined as relapsed within 12 months, have no good treatment options (Fisher 1979, Sehn 2012). In these patients, toxicity commonly outweighs the benefit of treatment with chemotherapy (Fisher 1979, Tinmouth 2001). Investigational agents (eg, ofatumumab, lenalidomide, bortezomib) have been used with response rates of 10% to 27%.

Due to the toxicity seen with standard combination treatment regimens in patients who are elderly, and for patients that have moderate tumor burdens and non-life threatening disease, a chemotherapy-free regimen such as ibrutinib and MEDI4736 may be an attractive treatment option if found to be well tolerated and have significant anti-tumor activity. Treatment options

with a favorable safety profile for recurrent disease in a heavily pretreated patient population are still needed.

1.3 Ibrutinib

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream BCR signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy, 3) CLL in patients with 17p deletion, and 4) Waldenstrom's Macroglobulinemia. Ibrutinib is currently under investigation in various indications.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B cells express cell surface immunoglobulins comprising the BCR, which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B cells. The BTK protein is expressed in most hematopoietic cells with the exception of T cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

Sixteen subjects enrolled in the dose-escalation phase of Study PCYC-04753 had a diagnosis of FL (Fowler 2012). Eleven subjects received ibrutinib at doses that achieved full BTK occupancy (ie, 2.5 mg/kg or higher). The median time on ibrutinib was 7 months (0 to 29 months) and time to response was 4.6 months. Overall, the response rate was 55% (3 CRs, 3 PRs; 95% confidence interval [CI]=[23%, 83%])(Fowler 2012) and the responses were durable (median response duration: 12.3 months) (Fowler 2012). Three patients had chemorefractory disease, and 2 of these patients responded (1 CR, 1 PR). The median PFS at study completion for subjects with FL was 13.4 months (Study PCYC-04753 CSR).

Ibrutinib has also demonstrated single agent activity in the treatment of relapsed or refractory de novo DLBCL in Study PCYC-1106-CA. Study PCYC-1106-CA is an ongoing Phase 2, open-label, nonrandomized, multicenter study in patients with relapsed or refractory de novo DLBCL receiving 560 mg/day of ibrutinib. Data are currently available on 70 patients from this trial who have relapsed or refractory disease with 29 ABC subtype, 20 GCB subtype, 16 Type 3 subtype and 5 subjects subtype unknown. The ORR in these 70 patients was 25% (17/70) with 9% of patients achieving a complete response (CR) and 16% of patients achieving a partial response (PR). Patients with ABC subtype appeared to be the most sensitive with an ORR of 41% (12/29) with 17% CR and 24% PR (de Vos 2013).

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure (IB).

1.3.1 Summary of Nonclinical Data

1.3.1.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (concentration that inhibits by 50% [IC_{50}] = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by cluster of differentiation (CD)69 expression (Herman 2011).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current IB.

1.3.1.2. Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related

corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and *in vivo* genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in subjects administered the dose of 560 mg daily, respectively.

1.3.1.3. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.3.1.4. Summary of Nonclinical Data (ibrutinib and MEDI4736 Combination)

This is an exploratory study and there are no nonclinical data on the combination of ibrutinib and MEDI4736.

1.3.2 Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the IB.

1.3.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after

overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance >30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

1.3.3 Summary of Clinical Safety

1.3.3.1. Monotherapy Studies in Hematologic Malignancies

Pooled safety data for subjects treated with ibrutinib monotherapy in 11 nonrandomized studies (PCYC-1102-CA, PCYC-1117-CA, PCYC-1112-CA [crossover only], PCYC-1104-CA, PCI-32765MCL2001, PCI-32765MCL4001, PCYC-1106-CA, PCYC-1111-CA, PCI-32765FLR2002, PCYC-04753, and PCI-32765-JPN-101) has been evaluated (ibrutinib IB, version 8.0).

The most frequently reported treatment-emergent adverse events (AEs) in more than 10% of subjects receiving ibrutinib as monotherapy in nonrandomized studies (N=1061) were diarrhea (35.9%), fatigue (28.6%), nausea (20.2%), cough (17.5%), and anemia (15.2%). The most commonly reported Grade 3 or 4 AEs that were hematologic in nature were neutropenia (10.7%), thrombocytopenia (6.2%), and anemia (5.5%). Pneumonia (5.7%), fatigue (2.9%), hypertension (2.7%), and atrial fibrillation (2.6%) were the most frequently reported nonhematologic Grade 3 or 4 AEs.

The incidence of treatment-emergent serious adverse events (SAEs) reported was 41.3% (N=1061); pneumonia (7.0%), atrial fibrillation (2.8%), and febrile neutropenia (2.3%) were the most commonly reported treatment-emergent SAEs.

In a randomized Phase 3 study in subjects with CLL/small lymphocytic lymphoma (SLL) (PCYC-1112-CA), the most frequently reported treatment-emergent AEs in the ibrutinib arm were diarrhea (47.7%), fatigue (27.7%), nausea (26.2%), pyrexia (23.6%), anemia (22.6%), and neutropenia (21.5%). AEs reported at a higher incidence (>10% difference) in the ibrutinib arm than in the ofatumumab arm included diarrhea (ibrutinib: 47.7%, ofatumumab: 17.8%), arthralgia (17.4%, 6.8%), and petechiae (13.8%, 1.0%).

The most commonly reported Grade 3 or 4 AEs in more than 2% of ibrutinib treated subjects that were hematologic in nature were neutropenia (16.4%), thrombocytopenia (5.6%), and anemia (4.6%). Pneumonia (6.7%) was the most frequently reported nonhematologic event. The most frequently reported SAEs in ibrutinib subjects were pneumonia (8.7%), atrial fibrillation (3.1%), pyrexia (3.1%), lung infection (2.6%), lower respiratory tract infection (2.1%) and urinary tract infection (2.1%).

The above information is reported based on available data from the ibrutinib IB, version 8.0, and is subject to change with more current updates. For more detailed information please refer to the current version of the IB.

1.3.4 Risks

1.3.4.1. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage, and hematuria.

1.3.4.2. Cardiac Events

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. In particular subjects with a history of cardiac arrhythmias should be monitored closely.

1.3.4.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

1.3.4.4. Diarrhea

Approximately one-third of subjects treated with ibrutinib monotherapy and two-thirds treated with combination therapy reported diarrhea. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe, with only a small number (0.1–1.5%) of Grade 3 events, and no Grade 4 events reported to date.

1.3.4.5. Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per Common Terminology Criteria for Adverse Events (CTCAE). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Isolated cases of John Cunningham (JC) virus reactivation resulting in progressive multifocal leukoencephalopathy

(PML) have been observed and resulted in death. Two cases in relapsed CLL subjects have been reported. One case occurred after multiple prior rituximab regimens and less than one year after the last dose of rituximab and high dose steroid administration. The second case occurred during concomitant administration of rituximab, bendamustine and ibrutinib.

1.3.4.6. Other Malignancies

Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Across the MCL (PCYC-1104-CA) and CLL/SLL studies (PCYC-1112-CA and PCYC-1102-CA), non-melanoma skin cancers and non-skin cancers were reported in 5.0% (18/357) and 2.5% (9/357) of subjects who received ibrutinib, respectively.

1.3.4.7. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. In a randomized Phase 3 study (PCYC-1112-CA), rash occurred at a higher rate in the ibrutinib arm than in the control arm. Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS), with a fatal outcome, was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and antigout medication (allopurinol) known to be associated with SJS.

1.3.4.8. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated LDH, bulky disease at baseline, and pre-existing kidney abnormalities.

1.3.5 Summary of Clinical Data (ibrutinib and MEDI4736 combination)

This is an exploratory study and there are no clinical data on the use of the combination of ibrutinib and MEDI4736 in FL or DLBCL.

1.4 MEDI4736

AstraZeneca and MedImmune are pursuing development of MEDI4736 as a potential anticancer therapy for patients with advanced malignancies. In addition to the information provided here, please refer to the MEDI4736 IB (Edition 7.0).

MEDI4736 is a human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], CD274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular

weight of approximately 149 kDa. MEDI4736 contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function (MEDI4736 IB).

1.4.1 Summary of Nonclinical Data

MEDI4736 binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. In vitro studies demonstrate that MEDI4736 antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN-γ). Additionally, MEDI4736 demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. In vivo studies show that MEDI4736 inhibits tumor growth in a xenograft model via a T-cell dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in >50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the PK, pharmacodynamics, and potential toxicity of MEDI4736. Following intravenous (IV) administration, the PK of MEDI4736 in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life ($t_{1/2}$) increased with increasing doses, suggesting saturable target binding-mediated clearance of MEDI4736. No apparent gender differences in PK profiles were observed for MEDI4736.

In general, treatment of cynomolgus monkeys with MEDI4736 was not associated with any MEDI4736-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK, pharmacodynamics, and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK, pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:MEDI4736 immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to MEDI4736. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of MEDI4736. Finally, data from the pivotal 3-month GLP toxicity study with MEDI4736 in cynomolgus monkeys showed that subchronic dosing of MEDI4736 was not associated with any

adverse effects. Therefore, the NOAEL of MEDI4736 in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of MEDI4736 to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues (MEDI4736 IB).

1.4.2 Summary of Clinical Data

As of the data cutoff date of 14 July 2014, a total of 509 subjects have been enrolled and treated with MEDI4736 in 10 ongoing clinical studies: 5 employing MEDI4736 as monotherapy and 5 as combination therapy (Table 1). No studies have yet been completed. The majority of the clinical data are from Study CD-ON-MEDI4736-1108, which has treated the largest number of subjects (N = 414).

Table 1. Overview of Ongoing Clinical Studies of MEDI4736 in Which Subjects Have Been Treated

Study Number (Phase)	Study Population	Treatment Regimen	Subjects Treated
Monotherapy Studies (N = 449)			
CD-ON-MEDI4736-1108 (Phase 1/2)	Advanced solid tumors	MEDI4736 Q2W or Q3W	414
D4190C00002 (Phase 1)	Advanced solid tumors	MEDI4736 Q2W or Q3W	18
D4190C00007 (Phase 1)	MDS	MEDI4736 Q2W	2
D4190C00003 (ATLANTIC) (Phase 2)	NSCLC	MEDI4736 Q2W	14
D4190C00001 (PACIFIC) (Phase 3)	NSCLC	MEDI4736 Q2W or placebo	1
Combination Therapy Studies (N = 60)			
CD-ON-MEDI4736-1161 (Phase 1)	Melanoma	MEDI4736 Q2W + trametinib ± dabrafenib	18
D4190C00006 (Phase 1b)	NSCLC	MEDI4736 Q2W or Q4W + tremelimumab Q4W	18
D791PC00001 (Phase 1)	NSCLC	MEDI4736 Q2W + gefitinib	10
D6020C00001 (Phase 1)	Advanced malignancies	MEDI4736 Q2W + MEDI0680 (AMP-514) Q2W or Q4W	4
LUD2013-003 (Phase 1)[a]	Advanced solid tumors	MEDI4736 Q2W + tremelimumab Q4W	10

MDS = myelodysplastic syndrome; NSCLC = non-small cell lung cancer; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks.

[a] All studies in this table are sponsored by AstraZeneca/MedImmune, except LUD2013-003, which is sponsored by the Ludwig Institute for Cancer Research.

Pharmacokinetics and Product Metabolism

MEDI4736 monotherapy exhibited nonlinear (dose-dependent) PK. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 15 mg/kg and approached linearity at ≥3 mg/kg, suggesting that the nonlinear PK of MEDI4736 is likely due to saturable target-mediated clearance. Exposures following multiple doses (currently up to a maximum of 26 doses) demonstrated accumulation consistent with PK parameters estimated from the first dose.

Suppression of free soluble PD-L1 (sPD-L1) was correlated with MEDI4736 PK concentrations. Following administration of MEDI4736 monotherapy, free sPD-L1 levels were below the lower limit of quantitation (LLOQ) in the majority of subjects with available data (n = 38) at all timepoints following IV doses ≥1 mg/kg every 2 weeks (Q2W). Overall, a low incidence of ADA was observed. Of the 220 subjects who received MEDI4736 monotherapy and for whom PK/ADA data were available, 5 were detected ADA positive, with an impact on PK and pharmacodynamics reported in 1 subject. None of the 16 subjects who received MEDI4736 in combination with tremelimumab were ADA positive (MEDI4736 IB).

1.4.3 Summary of Clinical Safety

As of 14 July 2014, no identified risks are clearly associated with the use of MEDI4736 (MEDI IB, Edition 7.0). Important potential risks based on the mechanism of action of MEDI4736 and its related molecules include immune-mediated reactions such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy. Additional important potential risks include infusion-related reactions, hypersensitivity, serious allergic reactions, serious infections, and immune complex disease.

The majority of the safety data are from the monotherapy study, CD-ON-MEDI4736-1108, specifically the 10 mg/kg Q2W cohort (N = 393). In this cohort, the most frequently reported (≥5% of subjects) AEs (all grades, regardless of causality) were fatigue (29.8%), nausea (20.1%), dyspnea (19.6%), decreased appetite (19.1%), constipation (14.0%), diarrhea and vomiting (12.5% each), cough (11.5%), pyrexia and back pain (10.4% each), rash (10.2%), headache (8.1%), dizziness (7.9%), anemia and pruritus (7.4 each), arthralgia (7.1%), myalgia and increased aspartate aminotransferase (AST) (6.6% each), peripheral edema and increased gamma-glutamyltransferase (GGT) (5.9% each), chills (5.3%), and increased alanine aminotransferase (AST) and musculoskeletal chest pain (5.1% each). In approximately half of the subjects, the highest AE severity was Grade 1 (25.2% of subjects) or Grade 2 (22.9% of subjects). Most of these events were managed clinically without the need for dose modifications or delays. Grade 3 or higher AEs that occurred in >1% of subjects were dyspnea (5.1%), increased GGT (3.3%), fatigue, general physical health deterioration, increased AST, and back pain (2.3% each), anemia and dehydration (1.8% each), and abdominal pain, vomiting, sepsis, syncope, and hypotension (1.3% each). Adverse events (all grades) considered by the

investigator to be related to MEDI4736 in >5% of subjects were fatigue (13.5%), nausea (8.4%), and diarrhea, rash, and decreased appetite (5.3% each). Treatment-related Grade 3 AEs in 2 or more subjects were fatigue (4 subjects), increased GGT (3 subjects), and vomiting, increased ALT, increased AST, and arthralgia (2 subjects each). There were 2 subjects with treatment-related Grade 4 events (hypercalcemia, fatigue) and 1 subject with a treatment-related Grade 5 event (angiopathy). In general, Grade 3 or 4 AEs were manageable with standard toxicity management guidelines.

SAEs and other significant AEs occurred in fewer than one-third of subjects treated with MEDI4736 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108. The most frequently reported SAEs (regardless of causality; >5 subjects) were dyspnea (3.6%), general physical health deterioration (2.2%), pyrexia (1.9%), back pain and abdominal pain (1.7% each), and dehydration and pleural effusion (1.4% each). One subject (with Stage IV lung cancer and a history of cardiac disease) died due to angiopathy considered by the investigator as related to MEDI4736. AEs that resulted in permanent discontinuation of MEDI4736 in ≥2 subjects were dyspnea (7 subjects), general physical health deterioration (5 subjects), and death, increased transaminases (AST and ALT), pulmonary embolism, and respiratory failure (2 subjects each).

Overall, the AE profile of MEDI4736 was consistent with the pharmacology of the target. No tumor types appeared to be associated with unique AEs (MEDI4736 IB).

1.4.4 Summary of Clinical Efficacy

As of 14 July 2014, partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00002) and 1 combination therapy study (D4190C00006, MEDI4736 and tremelimumab). Tumor assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria (Eisenhauer 2009). Clinical activity was observed across the 3 studies in solid tumors which include subjects with non-small-cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck (SCCHN), hepatocellular carcinoma (HCC), cutaneous melanoma, gastroesophageal cancer, and pancreatic adenocarcinoma.

1.5. Study Rationale

PD-L1 helps regulate normal immune responses by controlling T-cell activation and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir 2008; Park 2010). By binding to PD-L1, MEDI4736 inhibits PD-L1-dependent immunosuppressive effects and allows T cells to recognize and kill tumor cells (MedImmune/AstraZeneca, Data on file).

PD-L1 is expressed by DLBCL cells and PD-1 by DLBCL tumor-associated T cells (Rosenwald 2003, Xerri 2008). PD-L1 has been found to be highly expressed by immunohistochemistry in Epstein-Barr virus-positive DLBCL, which is correlated with an aggressive clinical course (Chen 2013). In a study of 288 DLBCL patients, those with an

elevated soluble PD-L1 level in plasma of at least 1.52 ng/mL experienced a poorer prognosis with a 3-year OS of 76% versus 89% ($p<0.001$) (Rossille 2014). Treatment of patients with DLBCL with pidilizumab, an anti-PD1 monoclonal antibody, showed an ORR of 51% with a CR rate of 34% (Armand 2013). PFS at 16 months was 72%, comparing favorably to other contemporaneously published clinical trials in a similar patient population (Gisselbrecht 2010, Vose 2011). Recently, a phase I study with nivolumab, another anti-PD monoclonal antibody, in heavily pretreated DLBCL patients showed an ORR of 36% (including 9% CR). (Lesokhin 2014)

In subjects with FL, PD1 is highly expressed on intratumoral and peripheral blood T cells and is associated with impaired T-cell function (Yang 2006, Myklebust 2013). In a phase 2 study testing pidilizumab in combination with rituximab in 32 subjects with relapsed FL, an objective response was reported in 66% of subjects with a 52% CR rate which is higher than expected for rituximab monotherapy in this patient population (Westin 2014). In addition, nivolumab has shown a 30% PR rate and 10% CR rate in heavily pretreated patients with FL that were included in a phase I trial (Lesokhin 2014). Therefore, targeting of the PD1/PD-L1 pathway might enhance endogenous antitumor responses in FL (Westin 2014).

Ibrutinib has demonstrated antitumor activity in DLBCL and FL (see Section 1.3). Treatment of subjects with DLBCL with ibrutinib has shown greatest benefit in the ABC subtype (de Vos 2013) which historically had been linked to a poorer prognosis compared to other subtypes. In addition to BTK inhibition, ibrutinib is an irreversible inhibitor of ITK (interleukin-2-inducible kinase) (Iwaki 2005, Dubovsky 2013). ITK is a member of the TEC family of kinases and retains close homology with the BTK active site including conservation of the cysteine residue which ibrutinib binds to covalently. ITK inhibition reduces helper T-cell (Th)2-dominant immune responses and potentiates Th1-based responses (Dubovsky 2013). This shift in the Th1/Th2 ratio may not only directly potentiate anti-tumor activity, but it may also augment anti-tumor immune activation triggered by MEDI4736.

Animal models of lymphoma have demonstrated activity when BTK and PD-L1 inhibitors are combined. BALB/c mice implanted with the syngeneic A20 B-cell lymphoma have been widely used to study immunotherapy for DLBCL and FL (Donnou 2012). A20 cells express BTK but are insensitive to ibrutinib in vitro and in vivo. In this model, a PD-L1 blocking antibody had modest effect on tumor growth whereas the tumor cells remained insensitive to ibrutinib. On combining the two antagonists, however, a complete tumor regression in 50% of treated animals was observed. Mechanistic studies implicated T cells as responsible for the tumor eradication. Mice treated with the combination therapy, but not with either single agent, mounted a robust and tumor-specific T-cell response. The superior efficacy of the ibrutinib/anti-PD-L1 combination was reproduced in a second model using the J558 plasmacytoma cells, which are also insensitive to ibrutinib. The results strongly suggest that ibrutinib has an immune-modulating property that enhances the anti-tumor effect of PD-L1 blockade (manuscript submitted).

Taken together, these data support testing the combination of ibrutinib and MEDI4736 for treatment of DLBCL and FL with the potential for synergistic anti-tumor activity.

1.6 Dosing Rationale

1.6.1 Ibrutinib Dose

Ibrutinib has been FDA-approved for previously treated MCL at a dose of 560 mg and for previously treated CLL and CLL with del17p at a dose of 420 mg daily. In 2 studies in subjects with B-cell malignancies, the pharmacodynamics of ibrutinib were determined by monitoring the BTK active-site occupancy in subjects' peripheral blood mononuclear cells (PBMC) before and after ibrutinib treatment (ibrutinib IB, version 8.0). Doses tested in the first-in-human ascending-dose study were 1.25, 2.5, 5.0, 8.3 and 12.5 mg/kg ibrutinib PO given non-continuously in 35-day cycles (28 days on, 7 days off) as well as 8.3 mg/kg and 560 mg ibrutinib PO given continuously (Advani 2013). No maximum tolerated dose (MTD) was identified. Subjects administered drug at doses of 2.5 mg/kg/day or higher achieved BTK occupancy at or above 90% at 4 and 24 hours after drug administration (Advani 2013). Absolute doses in the 2.5 and 5 mg/kg cohort ranged from 40 to 320 mg/day and from 280 to 600 mg/day, respectively. The highest dose administered was 1,400 mg of ibrutinib. Based on these data, fixed dose levels of >280 mg are expected to be necessary to ensure achievement of the full pharmacodynamic effect in the vast majority of patients. The sustained pharmacodynamic effect despite a relatively rapid elimination of ibrutinib is secondary to irreversible inhibition of BTK in subjects' PBMCs (ibrutinib IB, version 8.0). Consistent with this, once-a-day oral dosing resulted in 24-hour sustained target inhibition in these trials.

Ibrutinib has been tested in combination with R-CHOP in subjects with treatment-naïve DLBCL or FL in a Phase 1b study in which the recommended Phase 2 dose for ibrutinib was 560 mg per day (Younes 2014). The study demonstrated clinical activity across all dose cohorts in the all-treated population, with an ORR of 100% in evaluable DLBCL patients at the recommended dose (Younes 2014, Chaturvedi 2014). A Phase 3 trial of ibrutinib in combination with R-CHOP for frontline treatment of subjects with DLBCL at the 560 mg daily dose is ongoing.

Due to the extensive clinical experience with the 560 mg dose in terms of safety and efficacy, a dose of 560 mg/day has been chosen for the initial cohort in this study.

1.6.2 MEDI4736 Dose

In a phase I study, MEDI4736 has shown an acceptable safety profile using different doses and dosing schedules. Every-other-week doses of 0.1, 0.3, 1, 3, and 10 mg/kg MEDI4736 IV and one every-3-week dose of 15 mg/kg MEDI4736 IV were explored in a 12-month treatment period (Segal 2014). The highest individual dose delivered was 15 mg/kg; however, since this dose was given every 3 weeks, the highest total exposure was with 10 mg/kg MEDI4736 every 2 weeks (Segal 2014).

The majority of the safety data are from the monotherapy study, CD-ON-MEDI4736-1108, specifically the 10 mg/kg Q2W cohort (N = 393) (MEDI4736 IB). With respect to safety, no DLTs were reported in the dose-escalation portion of this trial and no MTD was identified. In approximately 50% of subjects, the highest AE severity was Grade 1 or Grade 2. Most of these events were clinically manageable without the need for dose modifications or dose delays. Serious adverse events (SAEs) and other significant AEs occurred in fewer than one-third of subjects treated with 10 mg/kg MEDI4736 given every other week. Across the currently ongoing MEDI4736 clinical studies, the incidence of infusion-related reactions has been low (0.8%; 4 of 509 subjects). In the monotherapy study, CD-ON-MEDI4736-1108, 5 infusion-related reactions were reported in 3 of 414 subjects (0.7%) treated with MEDI4736 every 2 or every 3 weeks. One subject had 3 Grade 2 events and the remaining 2 subjects had a Grade 2 and Grade 3 event, respectively. All events resolved, were nonserious, and considered related to MEDI4736 (MEDI4736 IB). Refer to Section 1.4.3 for additional details.

Consistent with the nonclinical studies, MEDI4736 exhibited nonlinear (dose-dependent) PK by peak concentration and AUC-time curve from 0 to 14 days over the dose range of 0.1 to 15 mg/kg, likely due to saturable target-mediated clearance. Near complete target saturation (membrane bound and sPD-L1) is expected with a ≥3 mg/kg dose of MEDI4736 given every 2 weeks. Exposures following multiple doses (currently data available up to a maximum of 26 doses) demonstrated accumulation that was consistent with PK parameters estimated from the first dose (MEDI4736 IB). Refer to Section 1.4.2 for additional details.

Preliminary population-PK modeling was performed using a nonlinear mixed-effects modeling approach (NONMEM, Version 7.1, ICON Development Solution, Elliott City, MD) using data from a total of 38 subjects. Based on the mean Michaelis constant (Km) value, >99% target saturation (both soluble and membrane bound) is expected at a concentration of MEDI4736 of ≥40 µg/mL. Hence, this concentration was identified as target trough concentration during dose selection. PK simulations indicate that following a 10 mg/kg dose of MEDI4736 given every 2 weeks, >90% of subjects are expected to maintain a PK exposure of ≥40 µg/mL throughout the dosing interval (MEDI4736 IB).

In multiple tumor types, early and durable clinical activity measured by tumor reduction was observed at multiple doses as early as 6 weeks and was maintained through 67+ weeks and off active therapy. The dose of 10 mg/kg every 2 weeks for 12 months was selected for further clinical development (Lutzky 2014).

Based on the data above, a dose of 10 mg/kg every 2 weeks for 12 months was chosen for the initial cohort in this study.

1.6.3 Ibrutinib and MEDI4736 Doses in Combination

Based on the above findings which describe the safety and PK profiles of ibrutinib and MEDI4736, the low discontinuation rate due to AEs, the low dose reduction rate, and the low

rate of high grade AEs, a dose of 560 mg ibrutinib PO daily continuously combined with a dose of 10 mg/kg MEDI4736 IV every 2 weeks for 12 months was chosen as the starting dose. (For MEDI4736 given every other week, the maximum number of doses is 24). As a lead-in to the first cycle, ibrutinib will be given for 7 days prior to starting MEDI4736 in order to obtain single agent PK and biomarker samples that can be compared to combination therapy. A dose de-escalation design will be employed and in each cohort a sentinel subject will have a 3-day observation period prior to dosing of subsequent subjects to monitor for unexpected acute or overlapping toxicities.

2. STUDY OBJECTIVES

2.1 Primary Objectives

Phase 1b:

- To determine the recommended Phase 2 dose (RP2D) of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas
- To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas

Phase 2:

- To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the ORR

2.2 Secondary Objectives

Phase 1b:

- To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the ORR
- To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the DOR
- To determine the PK and pharmacodynamics (ie, BTK) of both ibrutinib and MEDI4736 in subjects with relapsed or refractory lymphomas

Phase 2:

- To determine the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the DOR, PFS, and OS
- To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed and refractory lymphomas
- To determine the PK and pharmacodynamics (ie, BTK) of both ibrutinib and MEDI4736 in subjects with relapsed or refractory lymphomas

2.3 Exploratory Objectives

- To evaluate immune cell subsets after treatment with ibrutinib in combination with MEDI4736
- To evaluate non-BTK related pharmacodynamics (ie ITK) after treatment with ibrutinib in combination with MEDI4736
- To evaluate chemokine/cytokine levels after treatment with ibrutinib in combination with MEDI4736

- To identify genes and proteins associated with sensitivity or resistance to ibrutinib and/or MEDI4736 (ie, PD-L1)
- To evaluate the efficacy of ibrutnib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas by assessing the rate and duration of minimal residual disease (MRD) negativity

3. STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 1b/2, open-label multi-center study to assess the safety and efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory lymphomas. A 6+3 de-escalation design will be employed in Phase 1b to assess doses of ibrutinib in combination with MEDI4736 to determine the RP2D for this study.

3.1.1 Phase 1b

In the Phase 1b (safety portion) of the study, a starting dose of 560 mg of ibrutinib and 10 mg/kg of MEDI4736 will be explored in cohort 1 and will follow a 6+3 dose de-escalation design. Subjects will be enrolled in up to 4 dose cohorts (1, -1A, -1B, or -2) (for dose levels see Table 2). There is no requirement for a specific distribution of subjects with FL or DLBCL. The first subject in each dose cohort will be dosed as a sentinel subject with at least a 3-day observation period until the next subject in the cohort is dosed to monitor for any unexpected acute or overlapping toxicities.

Subjects with one of the following two tumor types will be eligible for enrollment:

- Follicular lymphoma (FL) (grade 1, 2, or 3A)
- Diffuse large B-cell lymphoma (DLBCL)

In cohort 1, ibrutinib will be administered orally (PO) daily in 6 subjects at a dose of 560 mg until unacceptable toxicity or disease progression occurs. As a lead-in to the first cycle, ibrutinib will be given for 7 days prior to starting MEDI4736 in order to obtain single agent PK and biomarker samples that can be compared to combination therapy. MEDI4736 will be administered at a dose of 10 mg/kg IV every 2 weeks in 28-day cycles for 12 months, or until unacceptable toxicity or disease progression occurs.

DLT assessment will occur from Day 1 of Cycle 1 of the combination therapy until the laboratory evaluations on Day 1 of Cycle 2 which will occur before the MEDI4736 infusion on Day 1 of Cycle 2. If subject incidence of DLTs within the DLT assessment period (with ibrutinib in combination with MEDI4736) is <33.3% (ie, ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2, and will be defined as the RP2D. If 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of 6-9 subjects experience a DLT, a dose de-escalation will occur. A similar 6+3 cohort design will be utilized in the dose de-escalation cohorts (see Table 2 and Section 5.2). De-escalation cohorts -1A and -1B will be opened simultaneously to determine which dosing schedule is most appropriate for the Phase 2 portion of the study. Determination will be based on the safety profile of the 2 treatment regimens, as evaluated by the Sponsor and enrolling investigators, potentially taking PK and pharmacodynamic aspects into consideration (see Section 12.11). If necessary, the dose de-escalation cohort -2 will be enrolled thereafter. The

process for dose level determination in Phase 1b to proceed to Phase 2 is summarized in Figure 1 (see also Section 5.2).

Table 2. Phase 1b Dosing Levels

28-Day Dosing Cycle	Ibrutinib[a]	MEDI4736[b]
Cohort 1	560 mg once daily PO	10 mg/kg IV
Cohort -1 A[c]	420 mg once daily PO	10 mg/kg IV
Cohort -1 B[c]	560 mg once daily PO	3 mg/kg IV
Cohort -2	420 mg once daily PO	3 mg/kg IV

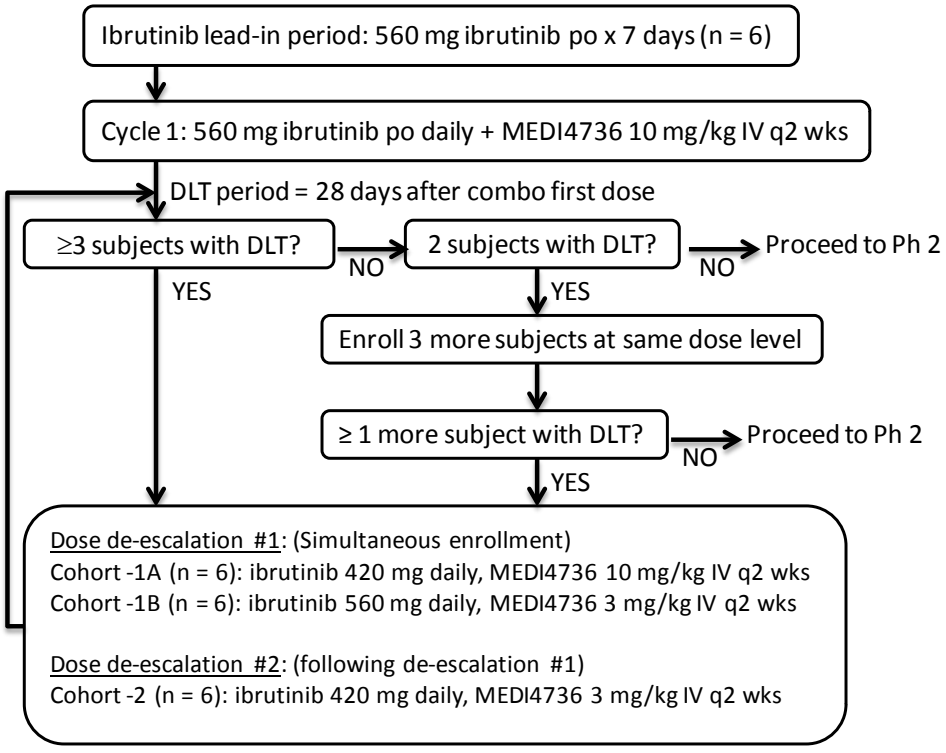
a. Ibrutinib will be administered PO daily beginning in the ibrutinib lead-in phase, then in combination with MEDI4736 starting Cycle 1 Day 1
b. MEDI4736 will be administered IV on Day 1 and Day 15 of each 28-day cycle
c. Cohorts -1A and -1B are 2 parallel cohorts and will be enrolled concurrently in the sequence of -1A followed by -1B

DLTs are defined in Section 5.3.

Replacement of subjects during the DLT observation period is defined in Section 5.4.

After the RP2D is defined, enrollment in Phase 2 will commence. Subjects who were not treated at the RP2D in Phase 1b will continue to be treated at the assigned dose and will be followed for response and overall survival.

Figure 1 Phase 1b Dose Level Determination



3.1.2 Phase 2

Subjects will be treated at the RP2D as determined in Phase 1b.

Two tumor types will be enrolled in separate cohorts as part of this protocol:

- Follicular lymphoma (FL) (grade 1, 2, or 3A)
- Diffuse large B-cell lymphoma (DLBCL)

FL: n = 39

The FL cohort will be enrolled prospectively without further subclassification. An interim analysis will be performed after 19 subjects are evaluable for tumor response after completing at least 2 response assessments (≥Cycle 6 Day 1). If only 6 or fewer responders (≤6/19) are observed, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment of responders) or tumor measurements (showing clinically relevant tumor reductions, ie, 40%, that fit the criteria for SD) may support continued enrollment (see Section 12.11). If a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject will be replaced (see Section 5.4).

DLBCL: n = 34

Subjects with GCB and non-GCB subtypes will be enrolled at a 1:1 ratio approximately. An interim analysis will be performed after 9 subjects are evaluable for tumor response after completing at least 2 response assessments (≥Cycle 6 Day 1). If only 1 or fewer responder (≤1/9) is observed, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment of responders) or tumor measurements (showing clinically relevant tumor reductions, ie, 40%, that fit the criteria for SD) may support continued enrollment (see Section 12.11). If a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject will be replaced (see Section 5.4).

In the DLBCL cohort, additional prospectively identified non-GCB subjects may be enrolled if a 22% ORR (2/9) is not achieved at the interim analysis in the unselected DLBCL population so that at least a total of 16 subjects with the non-GCB subtype are evaluated.

Note: The Phase 2 subjects include all of those subjects treated at R2PD in Phase 1b that have the tumor type as defined for Phase 2.

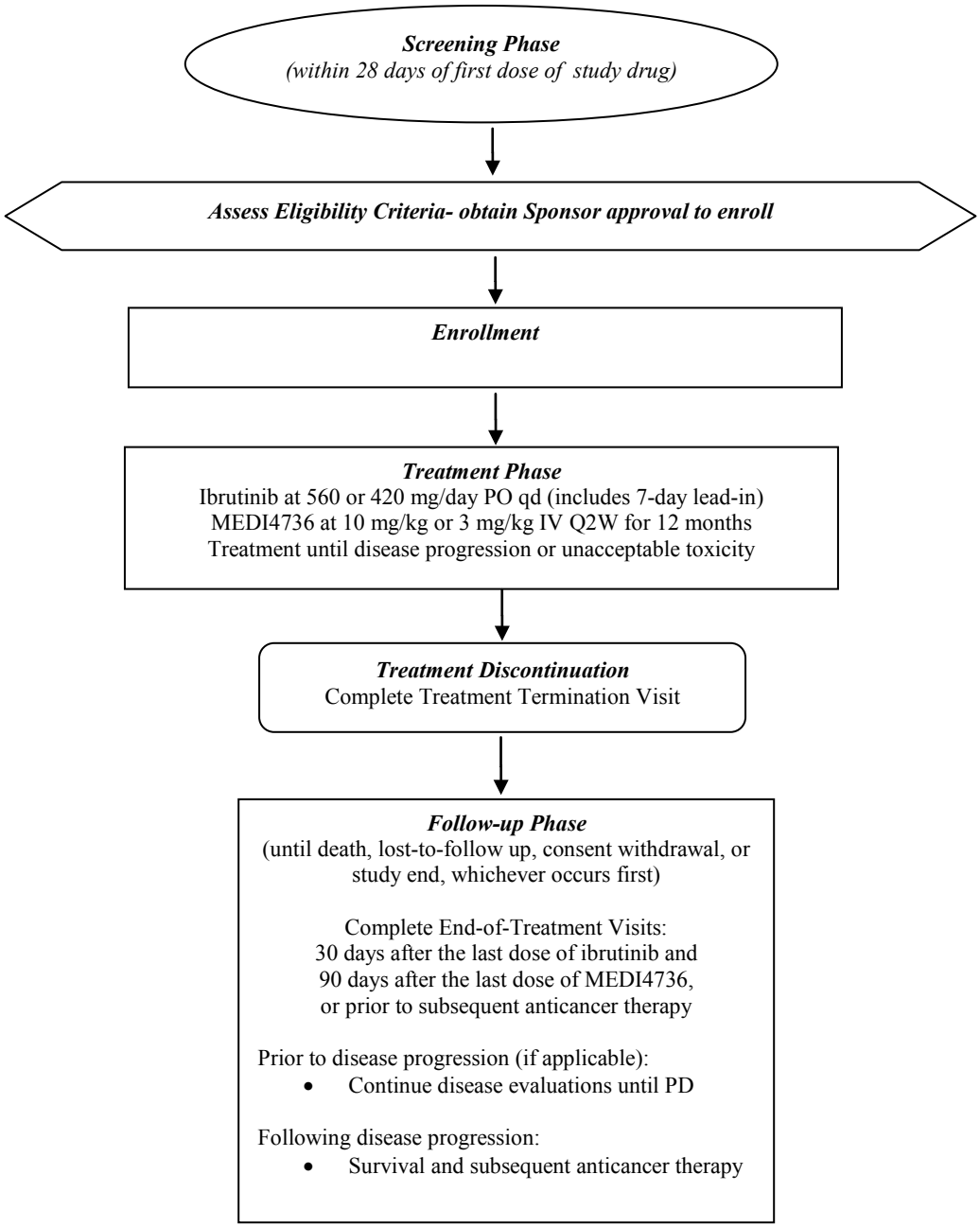
The primary analysis will occur at least 12 months after the last FL subject is enrolled and at least 9 months after the last DLBCL subject is enrolled.

Dosing of ibrutinib in combination with MEDI4736 will continue for a total of 12 cycles of therapy if the subject is deriving clinical benefit (CR, PR, or SD) and the subject is not experiencing unacceptable toxicity. After 12 cycles, dosing of ibrutinib alone will continue as long as clinical benefit is seen without safety concerns or disease progression.

Response evaluations will occur on Cycle 3 Day 1, Cycle 6 Day 1, Cycle 9 Day 1, Cycle 12 Day 1, and every 6 cycles thereafter. Assessment will follow the Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014).

In order to accommodate the potential for immune flare (pseudoprogression), treatment with MEDI4736 and ibrutinib may continue between the initial assessment of progression and confirmation for progression. Subjects with presumed PD who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive MEDI4736 and ibrutinib as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion (see Section 12.11). In the absence of clinically significant deterioration, a CT scan or biopsy may be performed at least 4 weeks later to confirm PD. If PD is confirmed at the later time point, PD should be assigned to the prior time point at which PD criteria were also met. MEDI4736 and ibrutinib should be discontinued if there is confirmed PD per Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014) or other clinical data suggest clear evidence of progression.

3.2 Study Schema



4. SUBJECT SELECTION

4.1 Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria:

1. Men and women ≥ 18 years of age
2. Pathologically confirmed:
   a) Phase 1b: diffuse large B-cell lymphoma or follicular lymphoma (grade 1, 2, or 3A) according to World Health Organization (WHO) criteria
   b) Phase 2: diffuse large B-cell lymphoma or follicular lymphoma (grade 1, 2, or 3A) according to WHO criteria without clinical or pathological evidence of transformation
3. Provision of a fresh tumor biopsy or an available archival tumor sample processed as formalin-fixed, paraffin-embedded (FFPE) taken within 3 months of screening, and after the most recent treatment (Note: Earlier archived tumor tissue from all enrolled subjects will also be requested.)
4. Relapsed or refractory disease:
   A. DLBCL
      1) Relapsed or refractory disease, defined as:
         a) Recurrence of disease after a complete response (CR),

         OR

         b) Partial response (PR), stable disease (SD) or progressive disease (PD) at completion of the treatment regimen preceding entry to the study (residual disease)
      2) Subjects who have not already had a stem cell transplant must not be considered a candidate for high dose chemotherapy with stem cell transplant (HDT/SCT) and must meet at least one of the following criteria:
         a) Age ≥70 years
         b) Diffuse lung capacity for carbon monoxide <50% by pulmonary function test
         c) Left ventricular ejection fraction <50% by multiple gated acquisition / echocardiogram
         d) Other organ dysfunction or co-morbidities precluding the use of HDT/SCT on the basis of unacceptable risk of treatment-related morbidity
         e) Failure to achieve PR or CR with salvage therapy
         f) Subject refusal of HDT/SCT

B. FL

1) Previously received at least one appropriate chemoimmunotherapy regimen and have relapsed or refractory disease

5. Measurable disease: One or more measurable disease sites on CT scan (>1.5 cm in longest dimension) is required. Lesions in anatomical locations (such as extremities or soft tissue lesions) that are not well visualized by CT may be measured by MRI instead.
6. Adequate hematologic function independent of transfusion support for at least 7 days prior to screening and independent of growth factor support for at least 14 days prior to screening, defined as:
   - Absolute neutrophil count >1500 cells/mm^3 (1.50 x 10^9/L)
   - Platelet count >50,000 cells/mm^3 (50 x 10^9/L) unless there is documented bone marrow involvement
   - Hemoglobin >8.0 g/dL
7. Adequate hepatic and renal function defined as:
   - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN)
   - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome such that bilirubin ≤3 x ULN or is of non-hepatic origin)
   - Estimated Creatinine Clearance ≥40 mL/min (Cockcroft-Gault)
8. Prothrombin time (PT) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
10. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation; OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
11. Male subjects who are not sterilized and who are sexually active with a female partner of childbearing potential, and female subjects of childbearing potential who are sexually active with a nonsterilized male partner must agree to use 2 highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, or intrauterine devices [IUDs]) during the period of therapy and for 3 months after the last dose of study drug (see Appendix 7).
12. Male subjects must agree to not donate sperm, and female subjects must agree to not donate eggs (ova, oocytes) for the purposes of assisted reproduction during or for 3 months after the last dose of either study drug.

4.2 Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

1. Anti-tumor therapy (chemotherapy, antibody therapy, immunotherapy, biologic-based therapy, or investigational agent) within 14 days of study Day 1 (or six weeks for nitrosureas or mitomycin C); Enrollment of subjects that have received molecularly-targeted small molecule inhibitors less than 28 days prior to study Day 1 will be permitted if more than 14 days and at least 5 drug half-lives have passed prior to receiving the first dose of ibrutinib.
2. Prior therapy with ibrutinib or other BTK inhibitor and/or anti-PD1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody
3. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03) grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of stable neuropathy, vitiligo, alopecia, or other irreversible toxicity not reasonably expected to be exacerbated by study treatment (eg, hearing loss)
4. Treatment with a strong cytochrome P450 (CYP) 3A inhibitor (see Appendix 4)
5. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug (Note: Subjects, if enrolled, should not receive live vaccines during the study and until 30 days after the last dose of study drug)
6. Current or prior use of immunosuppressive medication within 14 days before the first dose of MEDI4736. The following are exceptions to this criterion:
   - Intranasal, inhaled, topical corticosteroids, or local corticosteroid injections (eg, intra-articular injection)
   - Systemic corticosteroids at doses not to exceed 10 mg/day of prednisone or its equivalent
   - Corticosteroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication)
7. History of allogeneic organ transplant or <100 days after autologous transplant
8. Primary CNS lymphoma or evidence of CNS involvement by lymphoma
9. Any uncontrolled active systemic infection, or recent infection requiring intravenous antibiotic treatment that was completed ≤14 days before the first dose of study drug
10. Known history of previous clinical diagnosis of active tuberculosis
11. Known bleeding disorders (eg, von Willebrand's disease or hemophilia)
12. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
13. Major surgery within 4 weeks of first dose of study drug
14. Concomitant use of warfarin or other Vitamin K antagonists
15. History of primary immunodeficiency

16. Known history of human immunodeficiency virus (HIV) or current chronic/active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV)
    - Subjects with chronic or active hepatitis B as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction (PCR) may be performed and must be negative for enrollment.
17. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification (see Appendix 6); or a history of myocardial infarction, uncontrolled hypertension or cardiac arrhythmia, unstable angina, or acute coronary syndrome within 6 months prior to enrollment
18. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia formula
19. Unable to swallow capsules or malabsorption syndrome, disease or condition significantly affecting gastrointestinal function, or resection of the stomach or small bowel, or partial or complete bowel obstruction
20. Lactating women, men planning to father a child, or women planning pregnancy while taking study drug or within 3 months after the last dose of study drug
21. Known allergy or hypersensitivity to ibrutinib or MEDI4736 or any excipient
22. Active or prior documented autoimmune or inflammatory disorders including but not limited to inflammatory bowel disease (eg, colitis, Crohn's disease), diverticulitis with the exception of a prior resolved episode or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea, type I diabetes mellitus, multiple sclerosis, systemic lupus erythematosus, Wegener's granulomatosis (granulomatosis with polyangiitis), myasthenia gravis, Graves' disease, rheumatoid arthritis, pneumonitis, interstitial lung disease, hypophysitis, or uveitis within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
    - Subjects with vitiligo or alopecia
    - Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment
23. History of other malignancies, except
    - Malignancy treated with curative intent and with no known active disease present for ≥5 years before the first dose of study drug and felt to be at low risk for recurrence by the treating physician
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease
24. Unwilling or unable to participate in all required study evaluations and procedures
25. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at

undue risk, eg, psychiatric illness/social situations that would limit compliance with study requirement or compromise the ability of the subject to give written informed consent

26. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
27. Concurrent enrollment in another clinical study, unless in a follow-up period or in an observational study

5. TREATMENT OF SUBJECTS

5.1 Treatment Allocation

This is an open-label study (both Phase 1b and Phase 2). After the subject has completed all baseline (screening) procedures and meets the inclusion and none of the exclusion criteria, study site personnel can enroll the subject. All enrolled subjects will receive open-label ibrutinib capsules and MEDI4736 intravenous infusions.

In Phase 1b, two dose levels of ibrutinib (560 or 420 mg/day) and MEDI4736 (10 or 3 mg/kg IV every 2 weeks) may be tested (Table 2). The starting dose will be 560 mg of ibrutinib PO daily and 10 mg/kg of MEDI4736 IV every 2 weeks. The dose may be modified based on the number of DLTs observed. In each cohort, a sentinel subject will have a 3-day observation period prior to dosing of subsequent subjects to monitor for unexpected toxicities. In Phase 2, subjects will be treated at the RP2D as determined in Phase 1b.

5.2 Phase 1b Dose De-escalation and Stopping Rules

Refer to Figure 1 for a summary of the de-escalation process.

Phase 1b will follow a 6+3 design with 6-9 subjects at each dose level. Before determining the RP2D, 6 subjects in any given cohort must have completed the DLT observation period which is defined as the assessment period from Day 1 of Cycle 1 of the combination therapy until the laboratory evaluations on Day 1 of Cycle 2 which will occur before the MEDI4736 infusion on Day 1 of Cycle 2. The dose will be selected as the RP2D if the subject incidence of DLTs during the DLT assessment period with combination study treatment is <33% (ie, ≤1/6 or ≤2/9 subjects with a DLT). If there are ≥3 subjects with a DLT in Cohort 1, then the next lower dose level (Cohorts -1A and -1B, see Table 2) will be enrolled.

Cohort -1A and -1B are two parallel dose de-escalation cohorts and will be enrolled concurrently in a non-randomized fashion in the sequence of -1A followed by -1B. For example, the first available subject will go to Cohort -1A, the second subject to Cohort -1B, the third to -1A, the fourth to -1B, etc. However, when one dose de-escalation cohort needs an additional 3 subjects to evaluate DLTs, all available subjects will be assigned to this cohort first. In these cohorts, it will be determined which dosing schedule is most appropriate for the Phase 2 portion of the study. Determination will be based on the safety profile of the 2 treatment regimens, as evaluated by the Sponsor and enrolling investigators, potentially taking PK and pharmacodynamic aspects into consideration (see Section 12.11).

If the subject incidence of DLTs within the DLT assessment period with combination study treatment is <33.3% (ie, ≤1 of 6 or ≤2 of 9 subjects with a DLT), this dose level will be considered safe to proceed to Phase 2, and thus will be defined as the RP2D.

Enrollment in Cohort 1 will proceed as follows:

- If 0 or 1 DLT is observed during the DLT observation period in the initial 6 subjects in Cohort 1, then this dose will be the RP2D.
- If 2 DLTs are observed in the initial 6 subjects in Cohort 1, then 3 additional subjects will be enrolled to this cohort.
    - If 0 DLT in the 3 additional subjects is observed, then this dose will be the RP2D.
    - If 1 or more DLT is observed, the dose will be de-escalated to Cohorts -1A and -1B
- If 3 or more DLTs are observed in the initial 6 subjects, enrollment into Cohort 1 will be stopped and the dose will be de-escalated to Cohorts -1A and -1B.

A similar 6+3 cohort design will be utilized in the dose de-escalation cohorts. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter.

If a subject experiences a DLT during the DLT observation period, the subject will discontinue treatment. However, any subject(s) tolerating the dose level through the DLT observation period will continue with the same dose level of study drug even if subsequently-enrolled study subjects receive treatment at a dose de-escalation.

A Dose Level Review Committee (DLRC) will evaluate the safety data from each cohort of Phase 1b. Members of this committee will include participating investigators or designees as well as the Sponsor (invitees include: the Medical Monitor or designee, the clinical lead, a Drug Safety representative and a Biostatistician) (see Section 12.11).

5.3 Definition of Dose-Limiting Toxicity (DLT)

The assessment of DLT will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (accessible at the website, http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). The Phase 1b DLT observation period will occur from Day 1 of Cycle 1 of ibrutinib in combination with MEDI4736 treatment to the laboratory evaluations on Day 1 of Cycle 2 which will occur before the MEDI4736 infusion on Day 1 of Cycle 2.

A DLT is an AE at least possibly related to study drug(s) defined as:

1) Any Grade 3 or higher non-hematologic AE (with additional clarifications below)
    - Grade 3 or higher nausea, vomiting, or diarrhea (non-colitis-related) that is uncontrolled by maximal supportive care and persists for >7 days would be considered a DLT
    - Grade 3 fatigue that persists for >7 days would be considered a DLT
    - Any Grade 3 immune-related adverse event (irAE) that does not downgrade to Grade ≤2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids, or does not downgrade to Grade ≤1 or baseline within 14 days would be considered a DLT

- Any Grade ≥2 pneumonitis that does not resolve to Grade ≤1 within 3 days of the initiation of maximal supportive care would be considered a DLT.
- The DLT definition excludes the following conditions:
    - Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
    - Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
    - Vitiligo or alopecia of any AE grade would not be considered a DLT

2) Clinically relevant hematologic AE such as:
- Grade 3 or 4 neutropenia (ANC<1,000/ mm^3) lasting >7 days
- Febrile neutropenia (Grade 3 or 4 neutropenia with fever ≥38.3ºC)
- Grade 3 or 4 thrombocytopenia (<25,000/ mm^3) lasting >7 days or requiring transfusion or associated with Grade ≥2 bleeding
- Any other Grade 4 hematologic AE, except lymphopenia

5.4 Replacement of Subjects

During the Phase 1b DLT observation period, subjects will be replaced for any of the following reasons:

- Missed ≥5 consecutive doses of ibrutinib or missed 7 total doses (not due to DLT)
- Missed dose of MEDI4736 or received the MEDI4736 dose outside of the protocol-allowed window (±2 days) (not due to DLT)
- Study drug discontinuation for any reason other than DLT

Subjects who are replaced for missed doses may continue to receive study treatment if there is a clinical benefit, but they will not be part of the DLT analysis.

During the Phase 2 portion of the study, if a subject discontinues study drug prior to the first tumor response assessment for reasons other than progressive disease, the subject may be replaced.

5.5 Study Treatment

All eligible subjects will be treated with ibrutinib PO and MEDI4736 IV in 28-day cycles. Prior to the first cycle, ibrutinib will be given daily for 7 days in the ibrutinib lead-in period prior to starting MEDI4736. On infusion days where pharmacokinetic, pharmacodynamic, or biomarker samples are drawn post-dose, MEDI4736 IV should be given first, with administration of ibrutinib as soon as possible after the end of infusion.

Missed doses of ibrutinib and MEDI4736 will not be made up. Dose modification of MEDI4736 will not be permitted.

Dosing of ibrutinib will continue up to 3 years as long as the subject is deriving clinical benefit (CR, PR, or SD) and the subject is not experiencing unacceptable toxicity. Dosing of MEDI4736 will continue for a total of 12 cycles of therapy if clinical benefit is seen without safety concerns. Toxicity may result in discontinuation or hold of one study drug while the other may continue to be dosed. Depending on the suspected relatedness to either agent (or both), the Investigator may perform dose modification and/or dose delays as per Section 5.6.1.4 and/or Section 5.6.2.5 at his or her clinical discretion. Re-treatment with MEDI4736 will not be allowed following completion of 12 cycles of treatment, regardless of any dose delays, missed doses, or following permanent discontinuation for any reason.

5.5.1 Phase 1b

Two dose levels of ibrutinib (560 or 420 mg/day) and 2 dose levels of MEDI4736 (10 or 3 mg/kg IV every other week) may be tested. The starting dose will be 560 mg ibrutinib PO daily and MEDI4736 10 mg/kg IV every 2 weeks. Prior to the first cycle, there will be an ibrutinib lead-in period in which ibrutinib will be given for 7 days prior to starting MEDI4736.

The first subject in each dose cohort will be dosed as a sentinel subject with at least a 3-day observation period until the next subject in the cohort is dosed to monitor for any unexpected acute or overlapping toxicities.

Dose escalation of any agent (ibrutinib or MEDI4736) beyond the original assigned dose at any time will not be allowed.

5.5.2 Phase 2

Subjects will be administered ibrutinib in combination with MEDI4736 at the RP2D determined during the Phase 1b portion of the study. Prior to the first cycle, there will be an ibrutinib lead-in period in which ibrutinib will be given for 7 days prior to starting MEDI4736.

5.6 Study Medication

5.6.1 Ibrutinib

5.6.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. Study drug will be dispensed in child-resistant packaging.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.6.1.2. Dose and Administration

Ibrutinib 560 mg (4 x 140-mg capsules) or 420 mg (3 x 140-mg capsules) is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/ inducers and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 4).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose of ibrutinib will be administered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis unless otherwise specified in Section 8 and Appendix 1. Ibrutinib will be dispensed to subjects in bottles at appropriate visits. When new study drug is dispensed, unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) should be updated. Returned capsules must not be redispensed to anyone.

5.6.1.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose. There is no specific antidote for ibrutinib. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

Refer to Section 11 for further information regarding AE reporting.

5.6.1.4. Dose Modification for Adverse Reactions

For an ibrutinib-related adverse reaction, the dose of ibrutinib should be modified according to the dose modification guidelines in Table 3 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/μL) for more than 7 days. See Section 6.1 and 6.3 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelet count <50,000/mm^3 (50 x 10^9/L) in the presence of grade 2 or greater bleeding events.

- Grade 4 thrombocytopenia (platelet count <25,000/mm^3 (25 x 10^9/L).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anti-coagulants or anti-platelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.3).

Table 3. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 420 mg/day for original 560 mg/day dose; 280 mg/day for original 420 mg/day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day for original 560 mg/day dose) or discontinue for original 420 mg/day dose
Fourth	Discontinue study drug

After a dose reduction, dose escalations of ibrutinib to the previous higher dose may be considered after consultation with the Medical Monitor if the event does not recur after at least one cycle of the lower dose.

If tumor lysis syndrome is diagnosed, follow the institutional guidelines for management.

Study treatment should be discontinued in the event of an ibrutinib toxicity lasting more than 28 days, unless reviewed and approved by the Medical Monitor.

Study treatment interruptions, dose reductions or modifications, or any other changes in study drug administration should be recorded in the clinical database.

5.6.2 MEDI4736

5.6.2.1. Formulation/Packaging/Storage

Liquid Drug Product

MEDI4736 is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0. The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off

cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL. The solution will be diluted with 0.9% saline for IV infusion.

Unopened vials of MEDI4736 liquid Drug Product must be stored at 2°C to 8°C (36°F to 46°F).

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.6.2.2. Dose and Administration

The liquid product is to be diluted with 0.9% saline for IV infusion.

The first dose will be administered in the clinic on Cycle 1 Day 1 and then every 2 weeks thereafter.

MEDI4736 will be administered as an IV infusion approximately 1 hour in duration.

Following preparation of MEDI4736, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter. The IV line should be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered.

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessments (see Appendix 1). In the event of a Grade ≤2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a Grade ≤2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate (see Table 4 for toxicity management). Acetaminophen and/or an antihistamine (eg, diphenhydramine) or premedication per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade ≥3 in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.6.2.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any SAE criterion must be reported as a SAE in the appropriate time frame and documented as clinical sequelae to an overdose. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

Refer to Section 11 for further information regarding AE reporting.

5.6.2.4. Immune-related Adverse Events (irAEs)

Because MEDI4736 leads to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and MDX-1106 including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies (Brahmer 2010, Hodi 2010). Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection and PD), signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

5.6.2.5. Dose Modification for Adverse Reactions

For MEDI4736-related adverse reactions, please refer to the Table 4 below. It is important to note that these guidelines prepared by the Sponsor are to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities.

Table 4. Dose Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated MEDI4736-related Adverse Reactions

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
Immune-related Adverse Events (Overall Management)	Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.		It is recommended that management of irAEs follow the guidelines presented in this table – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, infections, etc.) – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events – Systemic corticosteroids (eg, prednisone or IV equivalent) should be considered for persistent
	Grade 1	No dose modification	
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	

Immune-Mediated Reactions			
	Dose Modifications		Toxicity Management
	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	low-grade or severe (Grade ≥3) events – If symptoms recur or worsen during corticosteroid tapering, increase the corticosteroid dose until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate – More potent immunosuppressives – TNF antagonist class (eg, infliximab), mycophenolate, etc. should be considered for events not responding to systemic steroids after discussion with study physician – Discontinuation of study drug is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumour response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes etc.)
	Grade 4	Permanently discontinue study drug/study regimen	
Infusion- related reactions		Any Grade	– Management per institutional standard at the discretion of investigator – Monitor subjects for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
	Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses
	Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event (up to 4 hours) Subsequent infusions may be given at 50% of the initial infusion rate	
	Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: – Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)
Pneumonitis/ Interstitial lung disease (ILD)		Any Grade	– Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan
	Grade 1	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only): – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated – Consider pulmonary and infectious disease consult
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2 (Mild to Moderate New Symptoms): – Monitor symptoms daily and consider hospitalization – Discuss with study physician and consider systemic steroids (eg, prednisone 1-2mg/kg/day or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup and treatment with IV methylprednisolone 2-4mg/kg/day should be considered – If no improvement within 3-5 days, further immunosuppressive therapy (eg, infliximab) should be considered. – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics – Consider pulmonary and infectious disease consult
	Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening): – Discuss with study physician – Pulmonary and infectious disease consult – Hospitalize the subject – Supportive Care (oxygen, etc.) – Initiate empiric IV corticosteroids (eg, methylprednisolone or equivalent) at 1 to 4 mg/kg/day – If no improvement within 3-5 days, additional workup and treatment with additional immunosuppressive therapy (eg, infliximab) should be considered – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Diarrhea/ Enterocolitis		Any Grade	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits)

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			– Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, etc.) – Steroids should be considered if an alternative etiology is not determined, even for low grade events, in order to prevent potential progression to higher grade event – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1	No dose modification	For Grade 1: – Close monitoring for worsening symptoms – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide – If event is persistent (>3-5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent – If not responsive within 3-5 days, consider IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day – If event is not responsive within 3-5 days or worsens, additional workup and treatment with IV methylprednisolone 2-4 mg/kg/day should be considered – If no improvement within 3-5 days, further immunosuppressives (eg, infliximab) should be considered – Consult study physician if no resolution to Grade ≤1 in 3-4 days – Once improving, gradually taper steroids over ≥4 weeks
	Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: – Discuss with study physician – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging as appropriate – Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day – If no improvement within 3-5 days, consider further immunosuppressives (eg, infliximab) – Caution: Ensure GI consult to rule out bowel perforation and refer to label before using

Immune-Mediated Reactions			
	Dose Modifications		Toxicity Management
			infliximab. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Hepatitis	Any Grade		– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications)
	Grade 1	No dose modification If it worsens, treat as Grade 2 event	– Continue LFT monitoring per protocol
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: – Discuss with study physician if no resolution to Grade ≤1 in 1-2 days – Recheck LFTs in 1-2 days. If event is persistent (>3-5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent – If no improvement within 3-5 days, consider additional workup and treatment with IV methylprednisolone 2-4 mg/kg/day o If no improvement within 3-5 days, consider further immunosuppressives (eg, mycophenolate mofetil) o Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 3	For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN - Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline - Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study	For Grade 3 or 4: – Discuss with the study physician – Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day o If no improvement within 3-5 days, consider further immunosuppressive therapy (eg, mycophenolate mofetil) o If still no further improvement within 3-5 days, consider other immunosuppressive therapy per local guidelines – Hepatology consult, abdominal workup, and imaging as appropriate o Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics

Immune-Mediated Reactions			
	Dose Modifications		Toxicity Management
		drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria	
	Grade 4	Permanently discontinue study drug/study regimen	
Rash (excluding Bullous skin formations)		Any Grade	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED**
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)
	Grade 2	For persistent (>1-2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to baseline then resume administration at next scheduled dose	For Grade 2 : – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening, discuss with study physician and consider systemic steroids prednisone 0.5 to 1 mg/kg/day or IV equivalent – Consider dermatology consult – Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen	For Grade 3 or 4: – Discuss with study physician – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consult dermatology – Consider skin biopsy (preferably more than 1) as clinically feasible. – Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism,		Any Grade	– Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and

Immune-Mediated Reactions			
	Dose Modifications		Toxicity Management
adrenal insufficiency, etc.)			weakness. – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs dependent on suspected endocrinopathy – If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor subject with appropriate endocrine function tests – If TSH <0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indiated and consider endocrinology consult
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: (including those with symptomatic endocrinopathy) – Discuss with study physician – Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For subjects with abnormal endocrine work up, consider short-term, high-dose corticosteroids (eg, methylprednisolone or IV equivalent) with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones) – For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated
	Grade 3	Hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Resume study drug/study regimen administration if controlled at the next	For Grade 3 or 4: – Discuss with study physician – Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day – Administer hormone replacement therapy as

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		scheduled dose	necessary – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Consult endocrinologist – Once improving, gradually taper immunosuppressive steroids over ≥4 weeks
	Grade 4	Permanently discontinue study drug/study regimen	
Immune-mediated Neurotoxicity (except Myasthenia Gravis and Guillian-Barre)		Any Grade	– Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.) – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	--
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1 For sensory neuropathy/ neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	– Discuss with study physician – Consider Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) – Consider systemic steroids prednisone 1-2 mg/kg/day or IV equivalent at 0.5 to 1 mg/kg/day – If no improvement within 3-5 days, consider additional workup and treatment with additional immunosuppressive therapy (eg, IVIgG)
	Grade 3	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days	For Grade 3 or Grade 4: – Discuss with study physician – Consult Neurology Consult – Consider hospitalization – Consider empiric IV corticosteroids (eg, methylprednisolone or IV equivalent) at 1 to 2 mg/kg/day – If no improvement within 3-5 days, consider additional workup and treatment with additional immunosuppressants (eg, IVIgG) – Once stable, gradually taper steroids over
	Grade 4	Permanently discontinue study drug/study regimen	

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			≥4 weeks
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis	Any Grade		– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative)
	Grade 1	No dose modification	– Discuss with the study physician – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Consider a neurology consult unless the symptoms are very minor and stable
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if does not resolve to Grade ≤1 within 30 days or if there are	Grade 2 : Moderate – Discuss with the study physician – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult

Immune-Mediated Reactions		
	Dose Modifications	**Toxicity Management**
	signs of respiratory insufficiency or autonomic instability	– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
	Grade 3 Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: – Discuss with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with

Immune-Mediated Reactions		
	Dose Modifications	**Toxicity Management**
	Grade 4 Permanently discontinue study drug/study regimen	plasmapharesis or IVIgG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
Non-immune Mediated Reactions		
CTC Grade/Severity	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study drug regimen until resolution to Grade ≤1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study drug regimen until resolution to Grade ≤1 or baseline For AEs that downgrade to Grade ≤2 within 7 days or resolve to Grade ≤1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the Sponsor	Treat accordingly as per institutional standard

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Abbreviations: AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal

MEDI4736 treatment interruptions in study drug administration should be recorded in the clinical database.

5.7 Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. For a list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

Subjects who withdraw for any reason other than those specified in Sections 5.4 and 9.2 will not be replaced. An End-of-Treatment Visit for ibrutinib (Section 8.3.1) and an End-of-Treatment Visit for MEDI4736 (Section 8.3.2) are required for all subjects except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from the time of ICF signing until 30 days after the last dose of ibrutinib and 90 days after the last dose of MEDI4736.

6.1 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with American Society of Clinical Oncology (ASCO) guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of corticosteroid treatment for non-cancer related medical reasons considered unrelated to study treatment (eg, unrelated joint inflammation, asthma exacerbation, rash, antiemetic use) at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted after discussion with the Medical Monitor. During corticosteroid treatment with >10 mg per day of prednisone or equivalent, MEDI4736 should be held until event resolution to Grade ≤1 or baseline; thereafter, MEDI4736 administration may be resumed at the next scheduled dose. For MEDI4736-related adverse reactions, please follow the corticosteroid and dose administration guidelines in Section 5.6.2.5.

6.2 Medications to Be Used with Caution

6.2.1 CYP3A-inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and $AUC_{0\text{-last}}$, of ibrutinib by 29- and 24-fold, respectively. The maximal observed ibrutinib exposure (AUC) was ≤2-fold in 37 subjects treated with mild and/or moderate CYP3A inhibitors when compared with the ibrutinib exposure in 76 subjects not treated concomitantly with CYP3A inhibitors. Clinical safety data in 66 subjects treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, and nefazadone) should be avoided. If a strong CYP3A inhibitor must be used, consider reducing the ibrutinib dose to 140 mg or withhold ibrutinib temporarily. Subjects should be monitored for signs of ibrutinib toxicity. If the benefit outweighs the risk and a moderate CYP3A inhibitor must be used, monitor subject for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix 4).

Co-administration of ibrutinib with a strong CYP3A inducer, rifampin, in healthy subjects decreases ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of

strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 4; 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.

6.2.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.2.3 Antiplatelet 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 6.4.

For subjects requiring the initiation of therapeutic anticoagulation therapy (eg, for treatment of atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and should 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. No dose reduction is required when study drug is restarted.

6.3 Prohibited Concomitant Medications

Any systemic chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving ibrutinib and/or MEDI4736 treatment.

Transfusional support is prohibited for at least 7 days prior to Screening. Growth factors are prohibited for at least 14 days prior to Screening.

Immunosuppressive medications within 14 days before the first dose of MEDI4736 and throughout the study are prohibited. The following are exceptions to this criterion:

- Intranasal, inhaled, topical corticosteroids, or local corticosteroid injections (eg, intra-articular injection)

- Corticosteroids as pre-medication for hypersensitivity reactions (eg, CT scan pre-medication)
- Corticosteroids given for prevention or treatment of infusion reactions
- Corticosteroids given for acute toxicity managements, eg pneumonitis or other immune-related AEs
- For the above exceptions, short courses (≤14 days) of systemic corticosteroid treatment for non-cancer related medical reasons at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted (see Section 6.1).

Subjects should not receive live vaccines during the study and until 30 days after the last dose of study drug.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.4 Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase the risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

6.4.1 Minor Surgical Procedures

For 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. There is no need to hold MEDI4736 for minor surgical procedures.

6.4.2 Major Surgical Procedures

For any 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. MEDI4736 has not been shown to affect wound healing; therefore, administration will not be impacted by major surgery.

6.4.3 Emergency 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.

7. STUDY EVALUATIONS

7.1 Description of Procedures

7.1.1 Assessments

7.1.1.1. ICF

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria (Section 4). De-identified copies of the pathology report confirming diagnosis of FL or DLBCL (tumor biopsy and bone marrow biopsy), a list of prior anticancer therapies and best responses, and the radiology report from screening CT scan (or MRI if indicated) and positron emission tomography (PET) will need to be submitted to the Sponsor as part of the enrollment process. In addition, DLBCL subtype should be provided (IHC testing at local laboratory) at the time of eligibility verification.

7.1.1.3. Medical History and Demographics

The subject's clinically significant medical history through review of medical records and by interview will be collected and recorded. *Clinically significant* is defined as any events, diagnoses or laboratory values requiring treatment, follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of the initial diagnosis and a list of all prior anticancer treatments, dates administered, and responses and duration of response to these treatments, will also be recorded.

7.1.1.4. Prior and Concomitant Medications

All prior/concomitant medications (including over-the-counter, supplements, and herbal products) and procedures will be collected from date of ICF or from 14 days before the start of study drug, throughout the End-of-Treatment Visit for ibrutinib, End-of-Treatment Visit for MEDI4736, or initiation of alternative cancer therapy, whichever is longer. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies will be collected until

death, subject withdrawal of full consent, loss to follow-up, or study termination by the Sponsor, whichever comes first.

7.1.1.5. Adverse Events

The accepted regulatory definition for an AE is provided in Section 11.1. All medical occurrences that meet the AE definition must be recorded from the time the ICF is signed until 30 days after the last dose of ibrutinib and until 90 days after the last dose of MEDI4736 or until initiation of alternative cancer therapy. AEs will be recorded in the eCRFs from the administration of the first dose of the study drug and will continue to be recorded until 30 days after the last dose of ibrutinib and until 90 days after the last dose of MEDI4736 or until initiation of alternative cancer therapy. Laboratory abnormalities designated clinically significant by the Investigator will also be recorded as AEs. A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- the abnormality is of a degree that requires active management; eg, change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.
- results in study withdrawal
- is associated with a serious adverse event
- is considered by the Investigator to be of clinical significance

Additional important requirements for AE and SAE reporting are explained in Section 11.4.

7.1.1.6. Physical Examination

Physical examination will be performed at Screening, Day 1 of each Cycle, End-of-Treatment visit for ibrutinib and End-of-Treatment Visit for MEDI4736. The physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

A limited symptom-directed physical examination is required at all other visits.

7.1.1.7. ECOG Performance Status

The ECOG performance index is provided in Appendix 3.

7.1.1.8. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

Vital signs will be measured repeatedly on MEDI4736 infusion days as outlined in Section 8. Additional measurements may be taken if a subject experiences an infusion reaction: 30 minutes, 60 minutes, and 2 hours post end of infusion.

7.1.2 Laboratory

Local laboratories will be used except for certain biomarker assays and in cases where a specialized laboratory is needed.

7.1.2.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported). These should be performed at the site's local laboratory.

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate. These should be performed at the site's local laboratory.

7.1.2.3. Thyroid Stimulating Hormone

Thyroid stimulating hormone (TSH) will be tested at the site's local laboratory. If TSH is abnormal, additional tests such as free thyroxine (T4) and triiodothyronine (T3) levels should be performed as clinically indicated.

7.1.2.4. Coagulation Studies

Measurement of prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT) will be performed at the site's local laboratory.

7.1.2.5. Creatinine Clearance

Creatinine clearance will be measured and calculated using the Cockcroft-Gault method or determined by 24-hour creatinine clearance collection. This should be performed in conjunction with the site's local laboratory.

7.1.2.6. Hepatitis Serologies and Human Immunodeficiency Virus (HIV)

Hepatitis serologies include Hepatitis C antibody, Hepatitis B surface antigen, Hepatitis B surface antibody, and Hepatitis B core antibody, and HIV-1 antibody will be evaluated. Subjects with chronic or active hepatitis B or C as diagnosed by serologic tests are excluded from the study. In equivocal cases, hepatitis B or C polymerase chain reaction (PCR) for viral load may be

performed and must be negative for enrollment. Subjects with a positive HIV screen and confirmatory test are excluded. These should be performed at the site's local laboratory.

7.1.2.7. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. The use of urine dipstick is permitted; however, if the dipstick demonstrates any abnormal parameters, microscopic examination of urine should be performed. This should be performed at the site's local laboratory. Urinalysis will be performed at Screening and throughout the MEDI4736 treatment period as outlined in Section 8.

7.1.2.8. Pregnancy Test

A serum pregnancy test will be required at Screening by local laboratory only for women of childbearing potential, as defined in the inclusion criteria. A urine pregnancy test will also be performed on Day 1 prior to the first dose of study drugs. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test will be performed routinely during and after study treatment and may be performed more frequently if required by local regulatory authorities.

7.1.3 Diagnostics/Procedures

7.1.3.1. ECG

Twelve-lead ECGs should be performed in triplicate with a 2- to 5-minute time lag between each measurement at Screening and for assessments throughout treatment as outlined in Section 8. ECGs should be performed at other times if clinically indicated.

Abnormalities noted at Screening should be included in the medical history. During visits in which both ECGs and blood draws are performed, ECGs are recommended to be performed first.

Additionally, triplicate 12-lead ECGs should be performed at the Investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new-onset dyspnea.

7.1.3.2. CT/MRI and PET Scans

A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites is needed for each response evaluation.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest and neck without contrast. In this case, neck nodes cannot be used as target lesions.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan

parameters, and includes the use of IV contrast. Also, in the event that the Sponsor requests submission of imaging, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET must be performed prior to the CT with IV contrast.

The same radiographic technique used for a subject's pretreatment tumor assessment should be used throughout the course of the study and should be mentioned in each radiology report. The same imaging equipment should be used for all scans, whenever possible.

Following the pretreatment tumor assessments, CT/MRI should be performed as per schedule of assessments in Appendix 1 (or more often if clinically indicated) and repeat PET scanning will only be required to confirm CR and will be performed only if it was positive at Screening.

Subjects who refuse CT/MRI scans and miss more than one scan will be removed from the study.

De-identified copies of all scans and radiology reports (including those from screening and any unscheduled scans) may be requested to be provided to the Sponsor or designee. At the Sponsor's discretion, the Sponsor or its designee may conduct an independent review of the Investigator responses.

7.1.3.3. Bone Marrow Aspirate and Biopsy

A unilateral bone marrow aspirate and biopsy will be done at Screening or up to 28 days before the first dose of study drug. Thereafter, bone marrow aspirate and biopsy will only be required to confirm CR if it was positive at Screening.

Standard clinical testing will be performed at the study center's local laboratory or other clinical laboratory listed on the Investigator's form FDA 1572. Additional samples will be collected for biomarkers and other exploratory evaluations such as for evidence of minimal residual disease (MRD) if methods are available.

All bone marrow (BM) samples obtained at Screening and to confirm CR should be submitted to the Sponsor if available.

7.1.3.4. Tumor Tissue Biopsy

Subjects are required to undergo a pre-treatment tumor biopsy which will be submitted to the Sponsor (unless archived formalin-fixed, paraffin-embedded [FFPE] tissue obtained within the last 3 months and after the last systemic anticancer treatment is available to submit to the

Sponsor) ("recent biopsy"). Earlier archived FFPE tissue for enrolled subjects will also be submitted to the Sponsor if available ("historical biopsy"). An optional biopsy will be collected at disease progression (see Section 6.4 for management of ibrutinib with invasive procedures).

Note the following guidelines for tumor biopsy sampling:

- If feasible, 4 core needle (at least 18-gauge) tumor biopsy samples are requested, with a minimum of at least 3 core samples. The first and third core samples will be placed in formalin and processed, while the second and fourth core samples (fourth sample, if available) will be immediately frozen and processed (see Laboratory Manual).
- An archived tumor tissue block (FFPE) where such samples exist in a quantity sufficient to allow for analysis will be requested for all enrolled subjects. If an archived tumor block cannot be provided, at least 10 newly cut unstained slides with tissue sections of 4 microns thick may be provided instead (see Laboratory Manual). Archived tumor tissue may be submitted from tumor biopsies starting from diagnosis.

Tumor biopsies may be evaluated for key target expression (eg, PD-L1) via IHC, and genomic analyses may be performed if there is sufficient material; other biomarkers that predict sensitivity or resistance to the drug combination may also be explored. At minimum, biopsy samples obtained at baseline (including archived slides) will be collected for FL and DLBCL subjects and used to determine GCB and non-GCB subtypes for subjects with DLBCL.

7.1.4 Pharmacokinetics/Pharmacodynamics/Biomarkers

Refer to the Laboratory Manual for instructions on collecting and processing these samples. On days of sampling visits, the clinical staff will instruct the subject to not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing. All predose collections should be performed prior to receiving any study drug (ibrutinib or MEDI4736). All post-dose collection times are calculated from the time that ibrutinib is dosed, unless subjects have discontinued ibrutinib and continue MEDI4736. If ibrutinib is discontinued, post-dose collection times will be calculated from the end of the MEDI4736 infusion.

7.1.4.1. Pharmacokinetics

Plasma concentrations of ibrutinib and serum concentrations of MEDI4736 will be determined using a validated analytical method. Other potential metabolites of ibrutinib may be explored. For collection timepoints, refer to the Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, and Biomarkers (Appendix 2).

7.1.4.2. Biomarkers and Pharmacodynamics Studies

Samples collected may be used for pharmacodynamic and biomarker assessments to monitor both ibrutinib and MEDI4736 activity when co-administered. Biomarkers of interest include BTK, ITK, and other kinase activity and signaling, soluble PD-L1, anti-drug antibody immunogenicity, drug occupancy, expression analysis, genomic sequencing, flow cytometry and secreted protein analyses (ie, chemokines, cytokines). Fluids including blood collected during the course of the study may be used for, but not limited to, pharmacodynamic and biomarker assessments as noted below. In addition, analyses of samples may be re-prioritized and other markers may also be investigated if new research emerges.

Cytokines, chemokines, cell surface markers and genomic markers may be tested in peripheral blood, tumor tissue and buccal swabs. If skin biopsies or other specimens are available, they may also be evaluated.

For molecular profiling of tumor samples, DNA/RNA may be extracted for gene expression and genomic testing including mutational analysis.

Immune cell subsets in peripheral blood may be evaluated by immunophenotyping, including T/B/NK cell counts and other markers.

Samples may be tested to evaluate potential biomarkers related to disease and treatment response, investigate potential mechanisms of treatment resistance, and assess the physiological effects of ibrutinib and MEDI4736.. These efforts may identify biomarkers that could assist with future development of this combination.

Immunogenicity analyses of anti-drug antibodies (ADA) will be performed before and after treatment with ibrutinib in combination with MEDI4736 to identify evidence of an anti-MEDI4736 response.

For collection timepoints, refer to the Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, and Biomarkers (Appendix 2).

7.1.4.2.1. Minimal Residual Disease (MRD) Analysis

Current data indicate that there may be a survival advantage in lymphoma patients who attain an MRD negative status at the completion of therapy (Mitterbauer-Hohendanner 2004, Liu 2012, Galimberti 2014). Results from several lymphoma studies including both indolent and malignant lymphomas have demonstrated such a trend. While not a part of the response criteria, collection of MRD will enhance the understanding of the depth of response achieved and may predict for impending relapse.

Baseline assessment for tumor burden (using the selected MRD assessment method) will be performed using tumor tissue biopsy, peripheral blood, and/or bone marrow aspirate collected at baseline.

Peripheral blood samples for MRD evaluation will be obtained at screening and throughout the study every 8 weeks until CR is achieved. For biomarker collection timepoints (including MRD evaluation), refer to the Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, and Biomarkers (Appendix 2).

Subjects with CR should have peripheral blood DNA samples obtained at the first time CR is suspected and every 3 cycles thereafter for evaluating MRD unless the subject withdraws consent or develops PD. Peripheral blood for MRD will be assessed every 3 cycles for 1 year.

In addition, BM aspirate samples obtained for CR confirmation may be assessed for MRD analysis unless the subject withdraws consent or develops PD. Instructions for collecting/submitting samples for MRD analyses are provided the Laboratory Manual.

7.2 Response Evaluations

Response assessments will be completed by the Investigator. The response criteria are based on the revised criteria for malignant lymphoma described by the International Working Group for NHL (Cheson 2014). At Screening, up to six target lesions will be selected and will be followed for the duration of the study until confirmed progressive disease.

For subjects with PET-positive tumors at baseline, response evaluations will largely be based on the CT scan; however PET will be required to confirm a complete response (CR).

Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead.

Refer to Appendix 5 for response criteria.

7.3 Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1 and Appendix 2) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

8. STUDY PROCEDURES

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments for Phase 1b and Phase 2 are provided in Appendix 1 with PK, pharmacodynamics, and biomarker collection details in Appendix 2.

8.1 Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window. The pre-treatment tumor tissue biopsy may be within 3 months.

8.1.1 Screening/Consenting Visit

The following procedures will be performed during Screening:

- Informed Consent
- Review of eligibility criteria (Inclusion/Exclusion criteria)
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vital signs, weight and height
- Triplicate 12-lead ECG (2-5 minutes apart)
- Bone marrow aspirate and biopsy
- Tumor biopsy (see Section 7.1.3.4)
- Review of prior and concomitant medications
- CT scan of neck, chest, abdomen, pelvis (and/or MRI for lesions not well-visualized by CT)
- PET scan (in addition to CT scan)
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance

- Serum pregnancy test (for women of childbearing potential only)
- Hepatitis serologies and HIV
- Urinalysis

- Research laboratory blood samples:
  - Ibrutinib biomarkers and pharmacodynamics

8.2 Treatment Phase

8.2.1 Ibrutinib Lead-in Day 1 (baseline)

Screening laboratory assessments performed within 48 hours of Ibrutinib Lead-in Day 1 may be used as pre-dose ibrutinib Lead-in Day 1 laboratory assessments and are not required to be repeated.

Pre-dose

- Confirmation of eligibility
- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Triplicate 12-lead ECG (2-5 minutes apart)
- Buccal swab
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Urine pregnancy test (for women of childbearing potential only)
- Research laboratory blood samples collected pre-dose for:
  - Ibrutinib pharmacokinetics
  - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- Dispense ibrutinib and diary card
- In-clinic administration of ibrutinib

Post-dose

- Research laboratory blood samples (see Appendix 2 for collection schedule):
  - Ibrutinib pharmacokinetics
  - Ibrutinib biomarkers and pharmacodynamics
- Triplicate 12-lead ECG (2-5 minutes apart) at approximately 2 hours post ibrutinib dose

- Review of AEs and concomitant medications

8.2.2 Ibrutinib Lead-in Day 2

Pre-dose

- Research laboratory blood samples collected pre-dose for:
  - Ibrutinib pharmacokinetics (24-hour time point from Day 1)
  - Ibrutinib biomarkers and pharmacodynamics (24-hour time point from Day 1)
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of ibrutinib

8.2.3 Ibrutinib Lead-in Day 6 or 7

Pre-dose

- Research laboratory blood samples collected pre-dose for:
  - Ibrutinib pharmacokinetics
  - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of ibrutinib

Post-dose

- Research laboratory blood samples (See Appendix 2 for collection schedule):
  - Ibrutinib pharmacokinetics
- Review of AEs and concomitant medications

8.2.4 Cycle 1 Day 1 (C1D1)

Pre-dose

- Complete physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Triplicate 12-lead ECG (2-5 minutes apart) 30-60 minutes prior to MEDI4736 infusion start
- Clinical laboratory tests for:
  - Hematology

- Serum chemistry
- TSH
- Urinalysis
- Urine pregnancy test (for women of childbearing potential only)

- Research laboratory blood samples collected pre-dose for:
  - Ibrutinib biomarkers and pharmacodynamics
  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics (includes anti-drug antibodies)
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoints:
  - End of MEDI4736 infusion (+5 minutes)
  - 30 minutes (±5 minutes) post end of MEDI4736 infusion
  - 60 minutes (±5 minutes) post end of MEDI4736 infusion
  - 2 hours (±15 minutes) post end of MEDI4736 infusion
- Triplicate 12-lead ECG (2-5 minutes apart) within 3 hours after the end of the MEDI4736 infusion
- Research laboratory blood samples (see Appendix 2 for collection schedule):
  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics (to be collected after ibrutinib dose is taken)
- Review of AEs and concomitant medications

8.2.5 Cycle 1 Day 8 (C1D8)

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology

- Serum chemistry

- Review of AEs and concomitant medications

8.2.6 Cycle 1 Day 15 (C1D15)

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Research laboratory blood samples:
  - Ibrutinib biomarkers and pharmacodynamics
  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Research laboratory blood samples (see Appendix 2 for collection schedule):
  - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

8.2.7 Cycle 1 Day 22 (C1D22)

- Physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology

- Serum chemistry

- Review of AEs and concomitant medications

8.2.8 Cycle 2 Day 1 (C2D1)

Pre-dose

- Complete physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - TSH
  - Urine pregnancy test (for women of childbearing potential only)
- Research laboratory blood samples:
  - Ibrutinib biomarkers and pharmacodynamics
  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics (includes anti-drug antibodies)
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Research laboratory blood samples (see Appendix 2 for collection schedule):
  - MEDI4736 pharmacokinetics
- Review of AEs and concomitant medications

8.2.9 Cycle 2 Day 15 (C2D15)

Pre-dose

- Physical exam

- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
- Research laboratory blood samples:
    - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
    - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications

8.2.10 Cycle 3 Day 1 (C3D1)

Pre-dose

- Complete physical exam
- Response Assessment
- CT scan of neck, chest, abdomen, pelvis (and/or MRI for lesions not well-visualized by CT) – can be performed within 7 days prior to C3D1
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Triplicate 12-lead ECG (2-5 minutes apart)
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - TSH
    - Urine pregnancy test (for women of childbearing potential only)
- Research laboratory blood samples:
    - Ibrutinib pharmacokinetics
    - Ibrutinib biomarkers and pharmacodynamics

  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics (includes anti-drug antibodies)
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Research laboratory blood samples (see Appendix 2 for collection schedule):
  - Ibrutinib pharmacokinetics
  - MEDI4736 pharmacokinetics
- Triplicate 12-lead ECG (2-5 minutes apart) at approximately 2 hours post ibrutinib dose
- Review of AEs and concomitant medications

8.2.11 Cycle 3 Day 15 (C3D15)

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry

  Note: After Cycle 3, Day 15 hematology and chemistry laboratories can be obtained if clinically indicated.
- Research laboratory blood samples:
  - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736

- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoints:
  - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications

8.2.12 Cycle 4 Day 1 (C4D1)

Pre-dose

- Complete physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - TSH
  - Urinalysis
  - Urine pregnancy test (for women of childbearing potential only)
- Research laboratory blood samples:
  - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications

8.2.13 Cycle 4 Day 15 (C4D15)

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoints:
    - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications

8.2.14 Cycle 5 Day 1 (C5D1)

Pre-dose

- Complete physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Triplicate 12-lead ECG (2-5 minutes apart)
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - TSH
    - Urine pregnancy test (for women of childbearing potential only)
- Research laboratory blood samples:
    - Ibrutinib biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card

- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoints:
  - End of MEDI4736 infusion (+5 minutes)
- Triplicate 12-lead ECG (2-5 minutes apart) 30-60 minutes within 3 hours after the end of MEDI4736 infusion
- Review of AEs and concomitant medications

8.2.15 Cycle 5 Day 15 (C5D15)

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications

8.2.16 Cycle 6 Day 1 (C6D1)

Pre-dose

- Complete physical exam
- Response Assessment
- CT scan of neck, chest, abdomen, pelvis (and/or MRI for lesions not well-visualized by CT) – can be performed within 7 days prior to C6D1
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology

- Serum chemistry
- TSH
- Urine pregnancy test (for women of childbearing potential only)

- Research laboratory blood samples:
  - Ibrutinib biomarkers and pharmacodynamics
  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics (includes anti-drug antibodies)
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications
- Research laboratory blood samples (see Appendix 2 for collection schedule):
  - MEDI4736 pharmacokinetics

8.2.17 Cycle 6 Day 15 (C6D15)

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:

- End of MEDI4736 infusion (+5 minutes)

- Review of AEs and concomitant medications

8.2.18 Day 1 of Each Subsequent Cycle

Subjects will continue to come in on Day 1 of each cycle for the first 12 months. After this time, subjects will come in on Day 1 of every third cycle. The following procedures will be performed unless otherwise specified.

Pre-dose

- Complete physical exam
- Response Assessment
- CT scan of neck, chest, abdomen, pelvis (and/or MRI for lesions not well-visualized by CT) should be performed every 3 cycles (Cycle 9, Cycle 12 and every 6 cycles thereafter)
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology (**every cycle through Cycle 12, then at every 3 cycles thereafter**)
  - Serum chemistry (**every cycle through Cycle 12, then at every 3 cycles thereafter**)
  - TSH (**every cycle through Cycle 12, then at every 3 cycles thereafter**)
  - Urinalysis (**on Cycle 7 and Cycle 10**)
  - Urine pregnancy test (for women of childbearing potential only) (**every cycle through Cycle 12, then at every 3 cycles thereafter**)
- Research laboratory blood samples (**on Cycle 7 and every 2 cycles thereafter, until CR achieved, then every 3 cycles thereafter**):
  - Ibrutinib biomarkers and pharmacodynamics
- Research laboratory blood samples (**on Cycle 9 and every 3 cycles thereafter**):
  - Ibrutinib biomarkers and pharmacodynamics
  - MEDI4736 pharmacokinetics
  - MEDI4736 pharmacodynamics (includes anti-drug antibodies)
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (±5 minutes) during MEDI4736 infusion
- Dispense ibrutinib and diary card (**every cycle through Cycle 12, then at every 3 cycles thereafter**)

- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Research laboratory blood samples (on **Cycle 9 and every 3 cycles thereafter**; see Appendix 2 for collection schedule):
  - MEDI4736 pharmacokinetics
- Review of AEs and concomitant medications

8.2.19 Day 15 of Each Subsequent Cycle

The Day 15 visits can be discontinued at the end of treatment with MEDI4736.

Pre-dose

- Physical exam
- ECOG Performance Status
- Vital signs (within 30 minutes of MEDI4736 infusion start) and weight
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 30 minutes (± 5 minutes) during MEDI4736 infusion
- In-clinic administration of ibrutinib (approximately within 15 minutes of end of MEDI4736 infusion)

Post-dose

- Vital signs at the following timepoint:
  - End of MEDI4736 infusion (+5 minutes)
- Review of AEs and concomitant medications

8.2.20 Response Evaluations

Response evaluations will be performed per the schedule outlined in Appendix 1. Imaging should be performed in the 7 days prior to the first dose of the next cycle. The following procedures will be performed in conjunction with standard visits as follows:

- CT scan of neck, chest, abdomen, pelvis (and/or MRI for lesions not well-visualized by CT)
- Response Assessment

- To be completed to confirm CR:
    - PET scan (in addition to CT scan)
    - Bone marrow aspirate and biopsy
    - Ibrutinib biomarkers and pharmacodynamics (unless already obtained within the last 7 days)

8.2.21 Treatment Termination (Optional Visit)

At the time of disease progression, an optional Treatment Termination visit may occur. The purpose of this visit is to allow an opportunity to collect biomarker samples and subject information at the time of disease progression prior to treatment discontinuation. If possible, the visit should be performed within 4 to 24 hours after the subject's previous dose. An optional tumor tissue biopsy may be collected at disease progression. In conjunction with this optional visit, CT or MRI and/or PET scans may be done per Investigator discretion to assess for PD.

The following procedures will be performed:

- Physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
- CT scan of neck, chest, abdomen, pelvis (if needed per Investigator discretion)
- PET scan (if needed per Investigator discretion)
- Response Assessment
- Tumor biopsy (if feasible) (see Section 7.1.3.4)
- Research laboratory blood samples:
    - Ibrutinib biomarkers and pharmacodynamics
    - MEDI4736 pharmacokinetics
    - MEDI4736 pharmacodynamics

8.3 Follow-up Phase

Once a subject has completed the Treatment Phase, they will enter the Post-treatment Phase. Subjects that withdraw from treatment for reasons other than progressive disease will participate in ongoing response follow-up discussed in Section 8.3.3.

8.3.1 End-of-Treatment Visit for Ibrutinib

An End-of-Treatment visit should occur 30 days (±7 days) after the last dose of ibrutinib or prior to the start of a new anticancer treatment. This visit may occur as a standard study visit if the

subject continues treatment with MEDI4736 alone. An optional tumor tissue biopsy may be collected if treatment was discontinued due to disease progression. If the subject starts a new anticancer treatment less than 7 days after the Treatment Termination visit, only those procedures not conducted at the Treatment Termination visit should be performed at the End-of-Treatment visit.

Subjects who withdraw consent to treatment may still participate in End-of-Treatment visit. The following procedures will be performed at the End-of-Treatment visit:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Triplicate 12-lead ECG (2-5 minutes apart)
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
- Research laboratory blood samples collected:
    - Ibrutinib biomarkers and pharmacodynamics (unless already obtained within the last 7 days)
- Review of AEs and concomitant medications

8.3.2 End-of-Treatment Visit for MEDI4736

An End-of-Treatment visit should occur 90 days (±7 days) after the last dose of MEDI4736 or prior to the start of a new anticancer treatment. This visit may occur as a standard Day 1 cycle study visit if the subject continues treatment with ibrutinib alone. Subjects who withdraw consent to treatment may still participate in the End-of-Treatment visit. The following procedures will be performed:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
    - Hematology
    - Serum chemistry
    - TSH
    - Urinalysis
    - Review of AEs and concomitant medications
- Research laboratory blood samples:
    - MEDI4736 pharmacokinetics

- MEDI4736 pharmacodynamics (includes anti-drug antibodies)

8.3.3 Response Follow-up

Subjects who discontinue the study treatments (both ibrutinib and MEDI4736) for reasons other than progressive disease will be followed every 12 weeks (±7 days) until progressive disease or death, up to 3 years after the first dose of the last subject enrolled. The following procedures will be performed:

- Physical examination
- CT scan of neck, chest, abdomen, pelvis (and/or MRI for lesions not well-visualized by CT) at the end of Cycle 2 (within 7 days prior to starting Cycle 3) and then again every third cycle (within 7 days prior to starting the next cycle)
- PET scan (if needed to confirm PD per Investigator discretion)
- Response assessment

8.3.4 Survival Follow-up

Once subjects progress or start use of alternative anticancer therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 12 weeks (±7 days) from the last dose by clinic visit or telephone to assess survival and the use of alternative anticancer therapy, up to 3 years after the last dose of the last subject enrolled. Subjects will be contacted until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

8.4 Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the Investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1 Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of study.

9.2 Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

- Progressive disease
- Unacceptable toxicity: an AE that prevents further administration of ibrutinib and MEDI4736 (including a DLT)
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an End-of-Treatment Visit and be followed for progression and survival.

The Investigator should notify the Sponsor within 24 hours if a subject discontinues ibrutinib and/or MEDI4736 treatment due to disease progression or a DLT and should provide redacted documentation of disease progression for review by the Sponsor's Medical Monitor. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed. These subjects should stay in the study to be followed for survival.

9.3 Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal;
- Whether the subject withdraws full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

10.1 Analysis Populations

10.1.1 Treated Population

The treated population will include subjects who have enrolled in the study and received at least 1 dose of any of the study treatments (either ibrutinib or MEDI4536). This population will be used for analysis of efficacy.

10.1.2 Safety Population

The safety population will consist of all enrolled subjects who received at least one dose of any study treatment. The safety population will be used for the analysis of safety data.

10.1.3 Response-evaluable Population

The response-evaluable population is defined as all enrolled subjects who received at least one dose of study treatment (ibrutinib or MEDI4736) and provided at least one post-baseline response (or disease) assessment. The response-evaluable population will be used as the primary population for analyses based on overall response.

10.1.4 Additional Analysis Populations

Additional analysis populations, which may be used in sensitivity analyses for primary and secondary efficacy objectives and for analyses of exploratory objectives, will be defined in the statistical analysis plan.

10.1.5 Replacement of Subjects

Subjects who were enrolled but not dosed or had missing doses as described in Section 5.4 will be replaced. For replacement of subjects in the DLT observation period please refer to Section 5.4.

10.2 Endpoints for Phase 1b

10.2.1 Primary Endpoints

- Recommended Phase 2 Dose (RP2D) of ibrutinib in combination with MEDI4736
- Safety and tolerability of ibrutinib in combination with MEDI4736

10.2.2 Secondary Endpoints

- Overall response rate (ORR)
- Duration of response (DOR)
- Pharmacokinetics (PK) and pharmacodynamics profiles

10.3 Endpoints for Phase 2

10.3.1 Primary Endpoint

- ORR

10.3.2 Secondary Endpoints

- DOR
- Progression-free survival (PFS)
- Overall survival (OS)
- PK and pharmacodynamics (ie, BTK) profiles

10.3.3 Exploratory Endpoints

- Immune cell subsets
- Non-BTK-related pharmacodynamics (ie, ITK)
- Plasma chemokine/cytokine levels
- Genes and/or proteins (within the tumor or other collected specimens) associated with sensitivity or resistance to ibrutinib and/or MEDI4736
- Rate and duration of MRD negativity

10.4 Sample Size Determination

This study is not powered for comparison of treatment arms. Approximately 109 subjects will be enrolled throughout the study (up to 36 subjects in Phase 1b and approximately 73 subjects in Phase 2).

10.4.1 Phase 1b

Dose de-escalation will follow the 6+3 design described in Section 3.1 and up to 4 cohorts including 3 dose de-escalation cohorts (1, -1A, -1B, and -2) will be enrolled if needed to determine the RP2D for the combination therapy.

A total of 6-36 subjects eligible for DLT assessment will be enrolled into Phase 1b of the study with 6-9 DLT-evaluable subjects (regardless of tumor type) per dose cohort. Subjects are considered DLT-evaluable if they receive the assigned dose of study treatment (both ibrutnib and MEDI4736) and complete the safety follow-up through the DLT-observation period.

Cohorts -1A and -1B are two parallel dose de-escalation cohorts. Subjects will be enrolled concurrently in the sequence of -1A followed by -1B. For example, the first available subject goes to -1A, the second to -1B, the third to -1A, the fourth to -1B, etc. However, when one dose de-escalation cohort needs an additional 3 subjects to evaluate DLTs, all available subjects will be assigned to this cohort first.

Subjects in Phase 1b who were dosed at the RP2D may also be included in the Phase 2 analysis.

10.4.2 Phase 2

Approximately 73 response-evaluable subjects (including those subjects treated at the RP2D in Phase 1b but with tumor type as defined for Phase 2) will be enrolled.

For FL:

A maximum of 39 response-evaluable subjects (including those subjects treated at the RP2D in Phase 1b but with tumor type of FL) will be enrolled. An interim analysis will be performed after 19 subjects are evaluable for tumor response after completing at least 2 response assessments. If only 6 or fewer responders (≤6/19) are observed, the Sponsor may consider discontinuation of this cohort (see Section 12.11).

The null hypothesis that the true ORR is 30% will be tested against a one-sided alternative that the ORR is 50%. The null hypothesis will be rejected if 17 or more responses are observed in 39 subjects. This design yields a 1-sided type I error rate of 0.05 and power of 80% when the true ORR is 50%. This statistical design including number of subjects and number of responders follows the statistical framework of Simon's minimax two-stage design (Simon, 1989). Enrollment will continue while the interim analysis is performed.

For DLBCL:

A maximum of 34 subjects with GCB and non-GCB subtypes (including those subjects treated at the RP2D in Phase 1b but with tumor type of GCB and non-GCB DLBCL) will be enrolled at a 1:1 ratio approximately.

An interim analysis will be performed after 9 subjects are evaluable for tumor response after completing at least 2 response assessments. If only 1 or fewer responder (≤1/9) is observed, the Sponsor may consider discontinuation of this cohort (see Section 12.11).

The null hypothesis that the true ORR is 15% will be tested against a one-sided alternative that the ORR is 35%. The null hypothesis will be rejected if 9 or more responses are observed in the 34 subjects. This design yields a 1-sided type I error rate of 0.05 and power of 80% when the true ORR is 35%. The statistical design including number of subjects and number of responders follows the statistical framework of Simon's optimal two-stage design (Simon, 1989). Enrollment will continue while the interim analysis is performed.

10.5 Subject Information

The distribution of subjects for each of the analysis populations will be provided. The number of subjects enrolled by each investigative site and country, dosed, and discontinued will be summarized. Treatment discontinuation will be summarized according to the reasons for discontinuation. Demographic and baseline variables will be summarized. Baseline disease characteristics will also be summarized.

10.6 Analysis Methods

Tumor response and disease progression will be based on tumor response assessment per the Investigator using the Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014). Criteria are summarized in Appendix 5.

10.6.1 Phase 1b Analyses

The primary objective of Phase 1b is to determine the RP2D and to evaluate safety and tolerability of ibrutinib in combination with MEDI4736. An algorithm-based 6+3 dose de-escalation design is used to find the RP2D of the combination regimen and to characterize the most frequent adverse events and DLTs. DLTs will be evaluated and will include all adverse events experienced through Phase 1b. Study-drug exposure and laboratory data will be evaluated and summarized by dose cohort.

The secondary objectives are to evaluate efficacy, PK, and pharmacodynamics in subjects receiving ibrutinib in combination with MEDI4736. The observed ORR along with the corresponding 95% confidence interval based on exact binomial distribution and duration of response (DOR) will be calculated and summarized with descriptive statistics by dose cohort and tumor type. PK and pharmacodynamics (ie, BTK) data will be summarized by dose cohort and tumor type.

10.6.2 Phase 2 Analyses

10.6.2.1. Primary Efficacy Analysis

The primary efficacy analysis will occur at least 12 months after the last FL subject is enrolled and at least 9 months after the last DLBCL subject is enrolled. The primary efficacy analysis will be based on ORR using the response-evaluable population in each of the two tumor cohorts. ORR is the proportion of response-evaluable subjects who achieved a complete response (CR) or a partial response (PR). The observed ORR along with its 95% confidence interval based on exact binomial distribution will be calculated and summarized for each tumor cohort.

10.6.2.2. Secondary Efficacy Analyses

Duration of response (DOR) is defined as duration of time from the date of initial response to the date of disease progression or the date of death due to any cause, whichever occurs first, and will be calculated and summarized with descriptive statistics for responders by tumor type cohort. The Kaplan-Meier estimate will be provided for DOR, if a sufficient number of responders are observed. The censoring rules for DOR will be provided in the SAP.

Progression-free survival (PFS) and overall survival (OS) will be evaluated by tumor type cohort with Kaplan-Meier estimates using the Safety Population. PFS is defined as duration of time from the first dose date of study drug (ibrutinib or MEDI4736) to the first documentation of disease progression per Investigator per Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014) or the date of death due to any cause, whichever occurs first. OS is defined as duration of time from the first dose date of study drug (ibrutinib or MEDI4736) to the date of death due to any cause. Censoring rules for PFS and OS will be described in the SAP.

Pharmacokinetics (PK) and pharmacodynamics (ie, BTK) profiles will be evaluated by tumor type cohort and overall.

10.6.2.3. Exploratory Efficacy Analyses

The exploratory efficacy variables will be summarized descriptively and may include the following:

- Immune cell subsets
- Non-BTK-related pharmacodynamics (ie, ITK)
- Plasma chemokine/cytokine levels
- Genes and/or proteins (within the tumor or other collected specimens) associated with sensitivity or resistance to ibrutinib
- Rate and duration of MRD negativity

10.6.2.4. Subgroup Analyses

For each tumor type cohort, a subgroup analysis will be conducted to calculate ORR and its 95% CI based on PD-1 ligand expression (positive versus negative).

For the DLBCL cohort, a subgroup analysis will also be conducted to calculate ORR and its 95% CI for GCB and non-GCB DLBCL types.

10.7 Safety Analysis

Analysis of safety data will be conducted on the safety population. The baseline value is defined as the last value collected on or prior to the first dose date of study drug (ibrutinib or MEDI4736, whichever comes first).

The safety variables to be analyzed include exposure of study drug, AEs, clinical laboratory test results (hematology and chemistry), ECOG performance, physical examination and vital sign measurements. Exposure of study treatment and reasons for discontinuation from study treatment will be tabulated. In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

10.7.1 Adverse Events

AE parameters to be evaluated are the type, incidence, and intensity of AEs; the relationship of AEs to study treatment; and the action taken with respect to study treatment due to AEs.

The verbatim terms used in the CRF by Investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) are those AEs occurring after the first dose of study treatment and within 30 days following the last dose of ibrutinib or within 90 days following the last dose of MEDI4736 (whichever date is later) OR will be collected until the start date of a new anticancer therapy that falls within this AE collection period; any AE that is considered study drug-related regardless of the start date of the event; or any AE that is present at baseline but worsens in severity or frequency after the first administration of study treatment or an AE that is subsequently considered drug-related by the Investigator. All TEAEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized. The number and percent of subjects with TEAEs will be summarized according to intensity (NCI CTCAE, Version 4.03) and drug relationship, as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or a serious AE.

10.7.2 Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Local laboratory results will be converted based on the normal ranges and standardized using the SI unit. Selected hematology and chemistry laboratory parameters are detailed in Section 7.1.2. Laboratory values will be graded using the NCI CTCAE Version 4.03.

Descriptive statistics will be provided for the values of selected clinical laboratory tests at each scheduled on-treatment evaluation including the final value. Percent change from baseline to each scheduled on-treatment evaluation and to the final value will also be summarized. For selected variables, the mean value and mean percent change over time will be presented graphically.

A summary of the shifts in selected laboratory hematology and serum chemistry parameters from baseline to the worst toxicity grade during the study will be provided. The worst toxicity grade during the study will be tabulated.

10.8 Dose Level Review Committee

A Dose Level Review Committee will be established to evaluate the safety data from each cohort of the Phase 1b on an ongoing basis. Members of this committee will include participating Investigators or designees as well as the Sponsor (invitees include: the Medical Monitor or designee, the clinical lead, a Drug Safety representative, and a statistician) (see Section 12.11).

10.9 Pharmacokinetic Analysis (Ibrutinib)

Ibrutinib and PCI-45227 bioanalytical data will be used in noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK summary.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227 (including but not limited to): C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$.

Mean plasma ibrutinib and PCI-45227 concentration time profiles will be plotted.

Ibrutinib data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population-PK analysis using nonlinear mixed effects models. For the population-PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population-PK analyses (if performed) will be presented in a separate report.

10.10 Pharmacokinetic Analysis (MEDI4736)

Individual MEDI4736 concentrations will be tabulated by dose cohort along with descriptive statistics. Individual and mean concentration-time profiles will be generated and included in the report. Pharmacokinetic parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined after the first or steady-state dose: peak concentration (Cmax), trough concentration (C_{trough}), time to peak concentration (T_{max}) and area under the curve (AUC), as data allow. Accumulation to steady state will be assessed as the ratio of $C_{max,ss}$:C_{max} and $C_{trough,ss}$:C_{trough}. Descriptive statistics of non-compartmental PK parameters will be provided.

10.11 Immunogenicity Analyses

Immunogenicity analyses will be performed by determining the anti-MEDI4736 response before and after after treatment with ibrutinib in combination with MEDI4736 at the time points outlined in Appendix 2.

10.12 Pharmacodynamic Analyses

Pharmacodynamic studies will be conducted to monitor both ibrutinib and MEDI4736 activity when co-administered. Blood samples will be collected at baseline and at selected time points outlined in Appendix 2. Pharmacodynamics assays for ibrutinib may include occupancy assays of BTK, ITK, or other targets in the blood or other relevant assays such as pITK/pPLCgamma in PBMCs. To monitor the activity of MEDI4736 after ibrutinib treatment, sPD-L1 will be evaluated at selected time points.

10.13 Biomarker Analyses

Clinically relevant biomarkers may be associated with clinical responses. Changes in phenotypic, genetic/genomic and molecular biomarkers may be evaluated over the course of ibrutinib and MEDI4736 treatment and will be summarized by treatment cohort. Association between baseline levels and changes from baseline in selected biomarkers and their response to treatment will be explored.

- Immune cell subsets in peripheral blood will be evaluated by immunophenotyping.
- Secreted protein levels (ie, chemokines, cytokines) in serum or plasma will be evaluated.
- Tumor biopsies will be evaluated for key target expression (eg, PD-L1) via IHC, and genomic analyses may be performed if there is sufficient material; other biomarkers that predict sensitivity or resistance to the drug combination may also be explored, including mutational analysis.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1 Definitions

11.1.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an AE term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

AEs may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE, unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention.

However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances, are also not SAEs.

- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2 Serious Adverse Events

An SAE 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 (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or the subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the Investigator believes that the event is serious, the event will be considered serious.

11.1.3 Severity Criteria (Grade 1-5)

Definitions found in the CTCAE v4.03 will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for

each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4 Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2 Unexpected Adverse Events

An "unexpected" AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as

anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3 Special Reporting Situations

Special reporting situations on a Sponsor study that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject exposure to the study drug, eg, name confusion)

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious and should be reported on the Serious Adverse Event Report Form. The SAE Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

11.4 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2 Adverse Event Reporting Period

All AEs, whether serious or non-serious, will be documented in the source documents from the time the signed and dated ICF is obtained until 30 days following the last dose of ibrutinib and 90 days following the last dose of MEDI4736. SAEs will be reported to the Sponsor from the time of ICF signing. Non-serious AEs will be recorded in the eCRF from the first dose of study drug until 30 days after the last dose of ibrutinib and 90 days following the last dose of MEDI4736. If both study drugs were discontinued at the same time, an SAE after 30 days and up to 90 days from the last dose of study drugs should indicate the causality for MEDI4736 only and N/A for ibrutinib (unless there is a causal relationship to ibrutinib).

SAEs reported after 30 days following the last dose of ibrutinib and 90 days following the last dose of MEDI4736 should also be reported if considered related to study drug. Resolution information after 30 days following the last dose of ibrutinib and 90 days following the last dose of MEDI4736 should be provided.

Subjects who discontinued investigational product for unacceptable AEs will be followed until there is a return to the subject's baseline condition, or until the Investigator considers that a clinically satisfactory resolution is achieved. Subjects will also be contacted to document any new onset AEs and follow any AEs that were ongoing at the time of investigational product discontinuation.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported (see Section 11.1.1).

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, the Investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of ibrutinib or 90 days after the last dose of MEDI4736, the death must be reported to the Sponsor as an SAE.

11.4.3 Expediting Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

All SAEs 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)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to local regulations.

The Investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 90 days after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a subject or subject’s partner from the time of consent to 90 days after the last dose of study drug. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE.

11.4.5 Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. Other malignancies will only be reported as an SAE if the event meets any serious adverse event reporting requirement listed under section "Serious Adverse Event" (otherwise captured as an AE in the eCRF).

11.4.6 Adverse Events of Special Interest (AESI)

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.6.1. Major Hemorrhage

Major hemorrhage is defined as:

- Any Treatment-emergent hemorrhagic adverse event of Grade 3 or higher.*
- Any Treatment-emergent serious adverse event of bleeding of any grade.
- Any Treatment-emergent central nervous system hemorrhage/hematoma of any grade.

* All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.6 above.

11.4.6.2. Pneumonitis

Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies (Brahmer 2012). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Additional assessments are to include pulmonary function tests and blood gases. Pulmonary consultation is recommended.

For Grade 2 pneumonitis that does not resolve to <Grade 1 within 3 days of maximal supportive care (including corticosteroids) or ≥Grade 3 pneumonitis, permanently discontinue MEDI4736.

11.4.6.3. Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PD-L1 and anti-PD-1 antibodies (Brahmer 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid

reactions against the monoclonal antibody, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnoea, cyanosis, respiratory failure, urticaria, pruritis, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheezing, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

11.4.6.4. Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer 2012). Inflammatory hepatitis has been reported in 3% to 9% of patients treated with anti CTLA-4 monoclonal antibodies (eg, ipilimumab). The clinical manifestations of ipilimumab-treated patients included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Cases where a subject shows AST or ALT ≥3 x ULN or total bilirubin ≥2 x ULN may need to be reported as SAEs. These cases should be reported as SAEs if after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. For potential Hy's Law and Hy's Law to be met, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in total bilirubin, but there is no specified time frame within which the elevations in transaminases and total bilirubin must occur.

Criteria for Hy's Law (FDA Guidance 2009):

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The Investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3 Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country-specific national regulations and/or local laws. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), **must** explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4 Quality Control and Quality Assurance

The Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

12.5 Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The Investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.6 Study Files and Record Retention

The Investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The Investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source

documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the Investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The Investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an Investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the Investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the Investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the Investigator for audit purposes.

12.7 Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The Investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exist within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator attests that the information contained in the CRFs is true by providing an electronic signature within the EDC system. After database lock, the

Investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving the data at the study site.

12.8 Investigational Study Drug Accountability

Ibrutinib and MEDI4736 used must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib or comparator to other Investigators, subjects, or clinics, or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

Accountability records for ibrutinib and MEDI4736 must be maintained and be readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number (PCYC-1136-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib dispensed and MEDI4736 administered for that subject
4. Date and quantity of drug dispensed or administered
5. Any unused ibrutinib returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

12.9 Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory

guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10 Investigator Responsibilities

A complete list of Investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the Investigator before commencement of the study. In summary, the Investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11 Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulations of the country in which the research is conducted. In summary, the Sponsor will select qualified Investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform

Investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

The study is being conducted by Pharmacyclics, Inc. in collaboration with partner companies, AstraZeneca and Janssen Research & Development, LLC (JRD), involved and informed in the execution of the study. When the Sponsor is engaged in making decisions regarding the combination of ibrutinib and MEDI4736 (eg, dose level selection, patient safety), the partner company AstraZeneca will have access to the data and actively participate in those decisions.

12.12 Financial Disclosure

A separate financial agreement will be made between each Principal Investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each Investigator and Subinvestigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13 Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

If a bodily injury is sustained, resulting directly from the use of the study drug, Pharmacyclics will reimburse for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury which is not covered by the subject's medical or hospital insurance, provided that the injury is not due to a negligent or wrongful act or omission by the Investigator/ study staff. The ICF will include a description of this reimbursement policy, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14 Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to

subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the Investigator and Pharmacyclics.

12.15 Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an Investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16 Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the Investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

13. REFERENCES

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14. APPENDICES

Appendix 1. Schedule of Assessments for Phase 1b and Phase 2

Study Visits	Screening	Treatment Phase (1 Cycle = 28 Days)														Post-treatment Phase			
		Ibrutinib Lead-in			Cycle 1				Cycle 2		Cycle 3		Cycle 4 & Beyond		Response Evaluation	Treatment Termination (optional)	End-of-Treatment		Response FU (Until PD)	Survival FU (Post-PD)
																	ibrutinib	MEDI4736		
		D1 Base-line	D2	D6 or D7	D1	D8	D15	D22	D1	D15	D1	D15	D1	D15	At C3D1, C6D1, C9D1, C12D1 & q6 cycles thereafter	At time of PD, ideally 4-24 h post last dose	30 d from last ibr dose or before next therapy	90 d from last MEDI dose or before next therapy	Q12 weeks from last CT/MRI	Q12 weeks from last dose
Visit Window	*-28 days*	*NA*	*±2 days*						*-2d*	*±2 days*					*-7 days*	*NA*	*±7 days*	*±7 days*	*±7 d*	*±7 d*
Procedures																				
Informed consent	X																			
Confirm eligibility (Inclusion/exclusion criteria)	X	X																		
Medical history & demographics	X																			
Physical exam	X	X			X	X	X	X	X	X	X	X	X	X[b]		X	X	X	X	
ECOG performance status	X	X			X	X	X	X	X	X	X	X	X	X[b]		X	X	X		
Vital signs[a] and weight (height only at screening)	X	X			X	X	X	X	X	X	X	X	X	X[b]		X	X	X		
Buccal swab		X																		
Bone marrow aspirate and biopsy	X														Required for CR					
Tumor Biopsy [i]	X															Optional at progression				
12-lead ECG (triplicate) – See Section 7.1.3.1 for details	X	X[j]			X[c]						X[j]		C5D1 only[c]				X			
Prior and concomitant medications	Continuous from ICF or 14 days prior the first dose of study drug (whichever is greater) to 30 days after last dose of ibrutinib/90 days after last dose of MEDI4736																			
Adverse events		Continuous from ICF to 30 days after last dose of ibrutinib and 90 days after last dose of MEDI4736																		
Hematology	X	X			X	X	X	X	X	X	X	X[d]	X[g]			X	X	X		
Serum chemistry	X	X			X	X	X	X	X	X	X	X[d]	X[g]			X	X	X		
TSH (see Section 7.1.2.3 if abnl)	X				X				X		X		X[g]					X		
Coagulation (PT, PTT, INR)	X																			
Creatinine clearance	X																			
Hepatitis serologies, HIV	X																			
Pregnancy test (serum at screening, urine at f/u)	X	X			For women of childbearing potential Q4 weeks from C1D1- C12D1, then Q3 cycles (±2 days)															
Urinalysis	X				X								X[f]					X		
PET scan	X														To confirm CR	X (if needed)			X (if needed)	

Study Visits	Screening	Treatment Phase (1 Cycle = 28 Days)														Post-treatment Phase			
		Ibrutinib Lead-in			Cycle 1				Cycle 2		Cycle 3		Cycle 4 & Beyond		Response Evaluation	Treatment Termination (optional)	End-of-Treatment		Response FU (Until PD)	Survival FU (Post-PD)
																	ibrutinib	MEDI4736		
		D1 Base-line	D2	D6 or D7	D1	D8	D15	D22	D1	D15	D1	D15	D1	D15	At C3D1, C6D1, C9D1, C12D1 & q6 cycles thereafter	At time of PD, ideally 4-24 h post last dose	30 d from last ibr dose or before next therapy	90 d from last MEDI dose or before next therapy	Q12 weeks from last CT/MRI	Q12 weeks from last dose
Visit Window	*-28 days*	*NA*	±2 days						*-2d*	±2 days					*-7 days*	*NA*	*±7 days*	*±7 days*	*±7 d*	*±7 d*
CT/MRI scan, also as clinically indicated	X										X				X	X (if needed)			X	
Response assessment											X				X	X			X	
Survival status and subsequent anticancer therapy																				X
Ibrutinib PK		See Appendix 2 for schedule																		
Ibrutinib biomarkers and pharmacodynamics	X	See Appendix 2 for schedule													At CR and/or progression	X	X			
MEDI4736 PK and pharmacodynamics					See Appendix 2 for schedule											X		X		
Study Drug Administration																				
In-clinic administration of MEDI4736 (give prior to ibrutinib daily dose)					X		X		X	X	X	X	X[e]	X[e]						
Dispense ibrutinib & diary card		X			X				X		X		X[g]							
In-clinic administration of ibrutinib		X	X	X	X		X		X	X	X	X	X[g]	X[e]						

abnl = abnormal, C = cycle, CR = complete response, CT = computed tomography, D or d = day(s), d/c = discontinuation, ECG = electrocardiogram, FU = follow-up, ibr = ibrutinib, h = hours, ICF = informed consent form, INR = international normalized ratio, MRI = magnetic resonance imaging, NA = not applicable, PD = progressive disease; PK = pharmacokinetics, PT = prothrombin time, PTT = partial thromboplastin time, TSH = thyroid stimulating hormone

Footnotes:

[a] Vital signs: On MEDI4736 infusion days, vital signs will be measured within 30 minutes prior to the start of MEDI4736 infusion, every 30 minutes (±5 minutes) during MEDI4736 infusion, and at the end-of- infusion of MEDI4736 (+5 minutes). On C1D1, vital signs will also be measured at 30 minutes (±5 minutes), 60 minutes (±5 minutes), and 2 hours (± 15 minutes) post end-of- infusion of MEDI4736. On C1D1, an additional 2-hour (±15 minutes) post MEDI4736 end-of-infusion ECG will be performed.

[b] And at Day 1 and Day 15 for every cycle thereafter. The Day 15 visits can be discontinued at the end of treatment with MEDI4736.

[c] To be performed within 30 minutes prior to start of MEDI4736 infusion and within 3 hours after end of MEDI4736 infusion

[d] After Cycle 3, Day 15 hematology and chemistry laboratories can be obtained if clinically indicated

[e] And at every cycle to Cycle 12 as long as MEDI4736 is administered

[f] And at every 3 cycles through Cycle 12

[g] And at every cycle through Cycle 12, then at every 3 cycles thereafter

[h] And at every cycle thereafter in the Treatment phase

[i] Earlier archived tumor tissue from all enrolled subjects will also be requested.

[j] Triplicate ECGs to be performed predose and at approximately 2 hours post ibrutinib dose

Appendix 2. Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, and Biomarkers: Phase 1b and Phase 2

Timepoint[a]			Ibrutinib PK	Ibrutinib Biomarker/ Pharmacodynamics [f]	MEDI4736 PK	MEDI4736 Pharmacodynamics
Screening				X		
Ibrutinib Lead-in	Day 1	Predose	X[g]	X		
		1 hr post dose (±15 min)	X			
		2 hr post dose (±15 min)	X[g]			
		4 hr post dose (±30 min)	X	X		
		6 hr post dose (±1 hr)	X			
	Day 2	Predose	X[b]	X[b]		
	Day 6 or 7	Predose	X[c]	X[c]		
		1 hr post dose (±15 min)	X			
		2 hr post dose (±15 min)	X			
		4 hr post dose (±30 min)	X			
		6 hr post dose (±1 hr)	X			
Cycle 1	Day 1	Predose		X	X	X (includes ADA)
		10 min (±5 min) after end of infusion			X	X (Collected after ibrutinib dose taken)
	Day 15	Predose		X	X	X
		4 hr post ibrutinib dose (± 30 min)		X		
Cycle 2	Day 1	Predose		X	X	X (includes ADA)
		10 min (±5 min) after end of MEDI infusion			X	
	Day 15	Predose		X		
Cycle 3	Day 1	Predose	X[e, g]	X[e]	X	X (includes ADA)
		10 min (±5 min) after end of MEDI infusion			X	
		1 hr post ibrutinib dose (±15 min)	X			
		2 hr post ibrutinib dose (±15 min)	X[g]			
		4 hr post ibrutinib dose (±30 min)	X			
		6 hr post ibrutinib dose (±1 hr)	X			
	Day 15	Predose		X		
Cycle 4	Day 1	Predose		X		
Cycle 5	Day 1	Predose		X		

Timepoint[a]			Ibrutinib PK	Ibrutinib Biomarker/ Pharmacodynamics [f]	MEDI4736 PK	MEDI4736 Pharmacodynamics
Cycle 6	Day 1	Predose		X	X	X (includes ADA)
		10 min (±5 min) after end of infusion			X	
Cycle 7 and then q2 cycles until CR, then q3 cycles thereafter	Day 1	Predose		X		
Cycle 9 and q3 cycles thereafter	Day 1	Predose		X	X	X (includes ADA)
		10 min (±5 min) after end of infusion			X	
Treatment Termination (optional)		At time of PD prior to treatment d/c		X	X	X
End-of-Treatment: after last ibrutinib dose	30 days post dose	±7 days		X (unless if already obtained within last 7 days)		
End-of-Treatment: after last MEDI 4736 dose	90 days post dose	±7 days			X	X (includes ADA)

Abbreviations: ADA = anti-drug antibodies; d/c = discontinuation; ibr = ibrutinib; CR = complete response; PD = progressive disease; PK = pharmacokinetics

Footnotes:

[a.] Record actual time of sample collection.
[b.] Sample collected 24 hours (±2 hours) after the ibrutinib lead-in Day 1 dose and prior to ibrutinib dosing on Day 2
[c.] Sample collected 24 hours (±2 hours) after the ibrutinib lead-in Day 5 dose and prior to ibrutinib dosing on Day 6, OR after the Day 6 dose and prior to ibrutinib dosing on Day 7, whichever is the PK collection day
[d.] Sample collected 24 hours (±2 hours) after the Cycle 1 Day 7 (C1D7) dose and prior to ibrutinib dosing on C1D8
[e.] Sample collected 24 hours (±2 hours) after the C2D28 dose and prior to ibrutinib dosing on C3D1
[f.] Includes MRD evaluation
[g.] Perform triplicate ECGs at predose and approximately 2 hours post ibrutinib dose to correspond with the ibrutinib PK blood draws (see Appendix 1)

Appendix 3. ECOG Performance Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 4, 2008.

Appendix 4. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.2.1 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/main-table/.

Appendix 5. Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014)

The following table provides a summary of response criteria for malignant lymphoma according to Cheson (2014). Please refer to published international guidelines for the most recent and complete details.

Table 6.1: Criteria for Response Assessment of Non-Hodgkin's Lymphoma

Response	Site	PET-CT-Based Response	CT-Based Response
Complete Response (CR)	Lymph nodes and extralymphatic sites	Complete metabolic response	Complete radiologic response (all of the following)
		Score 1, 2, or 3[a, b] with or without a residual mass on 5PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤1.5 cm in LDi No extralymphatic sites of disease
	Non measured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if determinate, IHC negative
Partial Response (PR)	Lymph nodes and extralymphatic sites	Partial metabolic response	Partial remission (all of the following)
		Score 4 or 5[b] with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 × 0 mm For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
	New lesions	None	None

Response	Site	PET-CT-Based Response	CT-Based Response
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease (SD)	Lymph nodes and extralymphatic sites	No metabolic response	Stable disease
		Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
	Non measured lesion	Not applicable	No increase consistent with progression
	Organ enlargement	Not applicable	No increase consistent with progression
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive disease (PD)	Individual target nodes/nodal masses	Progressive metabolic disease	Progressive disease requires **at least 1** of the following. PPD progression: An individual node/lesion must be abnormal with: • LDi >1.5 cm AND • Increase by ≥50% from PPD nadir AND • An increase in LDi or SDi from nadir: 0.5 cm for lesions ≤2 cm; 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
		Score 4 or 5 with an increase in intensity of uptake from baseline and/or meets criteria below for new FDG-avid foci	
	Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	
	Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any

Response	Site	PET-CT-Based Response	CT-Based Response
			axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
	Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

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

Footnotes:

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

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

Appendix 6. New York Heart Association (NYHA) Functional Classification

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Reference:
The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix 7. Contraception Requirements for MEDI4736

- Females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.
- Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as ≥60 years old and no menses for ≥1 year without an alternative medical cause).
- Subjects must use 2 acceptable methods of effective contraception as described in the table below.
- Nonsterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table below) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Effective methods of contraception (two methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (eg, Mirena®)	Combined pill
		Minipill
		Patch