PROTOCOL

TITLE:	A Multi-Center Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Durvalumab (MEDI4736), in Subjects with Relapsed or Refractory Solid Tumors
PROTOCOL NUMBER:	PCYC-1135-CA
STUDY DRUG:	Ibrutinib
IND NUMBER:	124674
SPONSOR MEDICAL MONITOR:	[redacted] Pharmacyclics LLC Phone: [redacted] Fax: Email:
SPONSOR:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521 United States of America
DATE FINAL:	11 December 2014
AMENDMENT 1 DATE:	05 February 2015
AMENDMENT 2 DATE:	26 June 2015
AMENDMENT 3 DATE:	18 December 2015

PROTOCOL APPROVAL PAGE

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Study Number: PCYC-1135-CA
Amendment 1 Date 05 February 2015
Amendment 2 Date 26 June 2015
Amendment 3 Date 18 December 2015

I have carefully read Protocol PCYC-1135-CA entitled "A Multi-Center Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, in Combination with Durvalumab (MEDI4736), in Subjects with Relapsed or Refractory Solid Tumors". 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 LLC 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 LLC representative is authorized to sign the protocol and any amendments:

[redacted] 20 December 2015

Medical Monitor [redacted] Date

[redacted]

Clinical Development, Pharmacyclics LLC

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SYNOPSIS

Study Title:	A Multi-Center Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib, in Combination with Durvalumab (MEDI4736) in Subjects with Relapsed or Refractory Solid Tumors
Protocol Number:	PCYC-1135-CA
Study Phase:	1b/2
Study Duration:	Estimated to be 3 years after the first dose of the last subject enrolled
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:	**Phase 1b:** **Primary Objectives:** • To determine the Recommended Phase 2 Dose (RP2D) or maximum tolerated dose (MTD) of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors • To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors **Secondary Objectives:** • To evaluate the efficacy of ibrutinib in combination with MEDI4736 by assessing the overall response rate (ORR) in subjects with relapsed or refractory solid tumors • To evaluate the efficacy of ibrutinib in combination with MEDI4736 by assessing the disease control rate (DCR) at Week 20 (Cycle 5) • To evaluate the efficacy of ibrutinib in combination with MEDI4736 by assessing the duration of response (DOR) • To determine the pharmacokinetics and pharmacodynamics of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors **Phase 2:** **Primary Objectives:** • To evaluate the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors by assessing the ORR **Secondary Objectives:** • To determine the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors by assessing the DCR at Week 20 (Cycle 5), 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 or refractory solid tumors

	• To determine the pharmacokinetics and pharmacodynamics of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors **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 kinase [ITK], Epidermal Growth Factor Receptor [EGFR]) 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/or proteins (within the tumor or other collected specimens) associated with sensitivity or resistance to ibrutinib and/or MEDI4736 (ie, PD-Ligand-1)
Study Design:	This is a Phase 1b/2, multi-center study to assess the safety and efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors. A 6+3 de-escalation design will be employed in Phase 1b to assess doses of ibrutinib in combination with MEDI4736 to determine the Recommended Phase 2 Dose (RP2D) or MTD for this study. **Phase 1b:** In the Phase 1b (safety portion) of the study, a starting dose of 560 mg of ibrutinib in combination with MEDI4736 will be explored in cohort 1 and will follow a 6+3 dose de-escalation design and will include a sentinel subject which will have a 3-day observation period prior to dosing of subsequent subjects. Subjects with one of the following three solid tumor types in Stage III/IV will be eligible for enrollment: • Non-small cell lung cancer (NSCLC) (adenocarcinoma or squamous-cell carcinoma) • Breast cancer (human epidermal growth factor receptor family member 2 [HER2] positive or triple negative) • Pancreatic cancer (adenocarcinoma) In cohort 1, (6 subjects, regardless of how many are of each tumor type), ibrutinib will be administered PO at a dose of 560 mg daily in combination with MEDI4736 at a dose of 10 mg/kg IV every 2 weeks in 28-day cycles until dose-limiting toxicity (DLT) or disease progression occurs. The DLT observation period includes Cycle 1 and laboratory assessments on Day 1 of Cycle 2 which will occur before the MEDI4736 infusion on Day 1 of Cycle 2. 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 subjects experience a DLT, dose de-escalation will occur. If subject incidence of DLTs during the first 28 days (Cycle 1=28 days and including laboratory assessments on Day 1 Cycle 2) of study treatment is <33.3% (ie, ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2, and defined as the RP2D. A similar 6+3 cohort design will be utilized in the dose 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. Determination of the RP2D will be based on the safety profile of the 2 treatment regimens. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter. A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic adverse event (AE) possibly related to study drug(s) occurring during the DLT observation period with the following clarifications for the toxicities below: • Grade 4 vomiting or Grade 3 nausea and vomiting despite maximum medical supportive care and persisting >3 days • Grade 3 or 4 diarrhea despite maximum medical supportive care and persisting >7 days • Grade 3 fatigue persisting >7 days • Grade 3 neutropenia lasting >7 days or with fever • Grade 3 infusion reaction that does NOT resolve with appropriate clinical management Subjects who discontinued study drug within Cycle 1 due to reasons other than DLT will be replaced for DLT assessment. After the RP2D is defined, enrollment in Phase 2 will commence. **Phase 2:** Subjects with one of three solid tumor types (Stage III/IV) will be enrolled in separate cohorts in the Phase 2 portion of this protocol: • NSCLC (adenocarcinoma and squamous-cell carcinoma at an approximate 2:1 ratio with at least 15 subjects with squamous-cell carcinoma) • Breast cancer (triple-negative and HER2-positive cancer) at an approximate 2:1 ratio with at least 15 subjects with the triple-negative breast cancer) • Pancreatic cancer (adenocarcinoma) For each of the above three cohorts, an interim analysis will be performed to evaluate the response and the safety profile. A cohort may be discontinued based on the interim efficacy and/or safety results. The decisions based on the results of the interim analysis are independent in the 3 individual disease cohorts. <u>NSCLC and breast cancer:</u> **Interim analysis:** n=18 per tumor type **Primary analysis:** n=43 per tumor type The NSCLC and breast cancer cohorts will enroll 18 subjects per tumor type for the interim analysis and 25 additional subjects per tumor type for the primary analysis (total n=43). An interim analysis will be performed after 18 subjects are evaluable for tumor response. If a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject will be replaced. If 2 or fewer responders are observed among the 18 evaluable subjects in a cohort, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers

	(that may aid in prospective enrichment for responders) or tumor measurements (showing clinically relevant tumor reductions, ie, <30%, that fit the criteria for stable disease [SD]) may support continued enrollment. Pancreatic cancer: **Interim analysis:** n=17 **Primary analysis:** n=44 For the interim analysis, 17 subjects will be enrolled, and 27 additional subjects will be enrolled for the primary analysis (total n=44). An interim analysis will be performed after 17 subjects are evaluable for tumor response. If a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject will be replaced. If 1 or no responder is observed among the 17 evaluable subjects, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment for responders) or tumor measurements (showing clinically relevant tumor reductions, ie, <30%, that fit the criteria for SD) may support continued enrollment. Subjects will receive ibrutinib and MEDI4736 continuously in 28-day cycles until progressive disease or unacceptable toxicity. Dosing of ibrutinib will continue as long as the subject is deriving clinical benefit (complete response [CR], partial response [PR], or SD) and the subject is not experiencing unacceptable toxicity. Dosing of MEDI4736 will continue for a total of 12 months of therapy if clinical benefit is seen without safety concerns. Assessment for response will occur at the end of Cycle 2 (Cycle 2 Day 28 [–7 days]) and then after every 3rd cycle (Cycle x Day 28 [–7 days]). Assessments will include computer tomography [CT]/magnetic resonance imaging [MRI] scans or physical examination (if the lesion is not assessable by CT/MRI) for the relevant tumor type and will follow RECIST 1.1 guidelines. In order to accommodate the potential for immune flare (pseudoprogression), treatment with ibrutinib and MEDI4736 may continue between the initial assessment of suspected progression and confirmation of progression. Subjects with suspected progressive disease who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive ibrutinib and MEDI4736 as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion. In the absence of symptomatic deterioration, a biopsy (if lesion is assessable) should be performed at the time of suspected tumor flare (in order to rule out tumor necrosis and/or an inflammatory reaction) or the investigator may continue dosing and a CT/MRI scan *or physical examination (if the lesion is not assessable by CT/MRI)* should 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 met. Ibrutinib and MEDI4736 should be discontinued if there is confirmed PD per RECIST 1.1 guidelines or other clinical data suggest clear evidence of progression (symptomatic deterioration).

Population:	Subjects with one of the following relapsed or refractory Stage III/IV solid tumors: • NSCLC (adenocarcinoma or squamous-cell carcinoma) or • Breast cancer (HER2 positive or triple negative) or • Pancreatic cancer (adenocarcinoma) Subjects with NSCLC or pancreatic cancer must have failed at least 1 prior first-line systemic therapy. Subjects with breast cancer must have failed at least 2 prior lines of systemic therapy.
Centers:	***Multi-center, US only***
Inclusion Criteria:	1. Pathologically confirmed: • Non-small cell lung cancer (NSCLC, adenocarcinoma or squamous-cell carcinoma) or • Breast cancer (HER2-positive by fluorescent in situ hybridization (FISH) or immunochemistry (IHC) [See Section 1.2 for definition] or triple negative) or • Pancreatic cancer (adenocarcinoma) 2. For Phase 2 only: Provision of a fresh tumor biopsy or an available archival tumor sample processed as FFPE (formalin-fixed paraffin embedded) taken within 3 months, and after the most recent treatment with the following exception: • For locally advanced pancreatic cancer, a fresh biopsy is not required if the tumor is inaccessible or the procedure places the subject at a safety risk. • No more than 10 subjects with locally advanced pancreatic cancer will be enrolled in the study without a biopsy. 3. Radiographically or clinically documented relapsed or refractory disease (Stage III or IV): Subjects with NSCLC or pancreatic cancer must have relapsed or refractory disease and must have failed at least 1 prior appropriate systemic first-line treatment regimen. Subjects with epidermal growth factor receptor (EGFR) mutation-positive NSCLC must have received an EGFR inhibitor and subjects with NSCLC that is anaplastic lymphoma kinase (ALK)-positive must have received an ALK inhibitor. Subjects with breast cancer must have relapsed or refractory disease and must have failed at least 2 prior appropriate systemic regimens. 4. One or more disease lesion on CT/MRI scan or by physical examination (if the lesion is not assessable by CT/MRI) that is measurable (ie, superficial soft tissue lesions, skin lesions, etc.) per RECIST 1.1 guidelines. 5. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening, with the exception of pegylated Granulocyte-colony stimulating factor (G-CSF) (pegfilgrastim) and darbepoetin which require discontinuation at least 14 days prior to screening defined as: • Absolute neutrophil count >1500 cells/mm^3 (1.50 x 10^9/L) • Platelet count >100,000 cells/mm^3 (100 x 10^9/L)

	• Hemoglobin >9.0 g/dL 6. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN) for subjects without liver metastases and ≤3.5 x ULN for subjects with liver metastases • Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) • Creatinine ≤2.0 x ULN and Creatinine Clearance ≥40 mL/min (Cockcroft-Gault or 24-hour creatinine clearance collection) 7. Prothrombin time (PT)/International normalized ratio (INR) <1.5 x upper limit of normal (ULN) and partial thromboplastin time (PTT)/ activated partial thromboplastin time (aPTT) <1.5 x ULN 8. Men and women ≥18 years of age 9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 10. Female subjects of reproductive potential must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year; 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 and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence [1], or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug (see Appendix 8). 12. Men must agree to not donate sperm and a woman 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 drug.

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Exclusion Criteria:	1. Subjects with tumors of mixed small cell and NSCLC histology 2. Any history of central nervous system (CNS) involvement of disease except as follows: Subjects with previously treated CNS metastases that are adequately treated with whole brain radiotherapy (+/- surgery), that are neurologically stable, and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to first dose of MEDI4736 plus ibrutinib. In addition, there must be no clear evidence of radiographically active disease for at least 90 days prior to study enrollment. 3. Anti-tumor therapy (chemotherapy, antibody therapy, immunotherapy, biologic-based therapy, molecularly-targeted therapy, radiation therapy or investigational agent) within 21 days of study Day 1 (six weeks for nitrosureas, mitomycin C, or antibody or molecular targeted agents with half-life ($t_{1/2}$) >10 days; 10 weeks for radio- or toxin-immunoconjugates); concurrent use of hormone deprivation therapy including but not limited to anastrozole, letrozole, or tamoxifen citrate for breast cancer and hormonal replacement therapy for non-cancer-related conditions is permitted. Enrollment of subjects that have received molecularly-targeted small molecule inhibitors less than 21 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. 4. Prior treatment with ibrutinib or other BTK inhibitor anti-CD137 or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody. The following are exceptions to this criterion: • Subjects previously treated with an anti-PD1, anti-PD-L1, or anti-PD-L2 antibody 5. Known allergy or hypersensitivity to ibrutinib or MEDI4736 or any excipient 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. 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 1 diabetes mellitus; multiple sclerosis; systemic lupus erythematosus; Wegener's granulomatosis; myasthenia gravis; Graves' disease; rheumatoid arthritis; hypophysitis; uveitis; etc) 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's thyroiditis) stable on hormone replacement therapy or psoriasis not requiring systemic treatment 8. History of allogeneic organ transplant 9. 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 10. 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 and alopecia or other irreversible toxicity not reasonably expected to be exacerbated by study treatment (eg, hearing loss) 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. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug (Note: Subjects, if enrolled, should not receive live vaccines during the study and until 180 days after the last dose of study drugs) 14. Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug 15. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. 16. History of primary immunodeficiency 17. Known history of previous clinical diagnosis of tuberculosis 18. Any uncontrolled active systemic infection or pneumonitis or interstitial lung disease 19. Major surgery within 4 weeks of the first dose of study drug 20. 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. 21. 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 (Appendix 7); or a history of myocardial infarction, uncontrolled

	hypertension or cardiac arrhythmia, unstable angina, or acute coronary syndrome within 6 months prior to enrollment 22. Unable to swallow capsules or active malabsorption syndrome not controlled by medication, disease or conditions significantly affecting gastrointestinal function, or complete resection of the stomach, or complete resection of small bowel, or partial or complete bowel obstruction. 23. Concomitant use of warfarin or other Vitamin K antagonists 24. Treatment with a strong cytochrome P450 (CYP) 3A inhibitor 25. Pregnant or lactating female; men planning to father a child or women planning a pregnancy while taking study drug or within 3 months after the last dose of study drug 26. Concurrent enrollment in another clinical study, unless in a follow-up period or it is an observational study. 27. Unwilling or unable to participate in all required study evaluations and procedures 28. 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)
Study Treatment:	One cycle of treatment is 28 days in duration and consists of daily administration of ibrutinib PO in combination with MEDI4736 IV every 2 weeks. Dosing of MEDI4736 will continue for a total of 12 months if clinical benefit is seen without safety concerns. Re-treatment with MEDI4736 will not be allowed following completion of 12 months of treatment, regardless of any dose delays, missed doses, or following permanent discontinuation for any reason. Dosing of ibrutinib will continue as long as the subject is deriving clinical benefit (CR, PR, or SD) and the subject is not experiencing unacceptable toxicity. **Phase 1b:** Subjects in one cohort may all be of the same tumor type in Phase 1b. 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 *Cohorts -1A and -1B are two parallel cohorts. Subjects will be enrolled into those two cohorts concurrently. **Phase 2:** Recommended Phase 2 Dose (RP2D) established in Phase 1b (ibrutinib 420 mg or 560 mg PO daily, and MEDI4736 3 mg/kg or 10 mg/kg IV every 2 weeks) given in 28-day cycles in the three tumor type cohorts.
Safety Plan:	This study will be monitored in accordance with the Sponsor's Pharmacovigilance Procedures. Adverse events (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 (DLRC) will evaluate the safety data from each cohort of the Phase 1b. Members of this committee will include participating investigators or designees as well as

	the Sponsor (at a minimum: the Medical Monitor or designee, a Drug Safety representative and a Biostatistician). The safety profile will also be evaluated at the interim analysis in the Phase 2 portion of the study.
Statistical Methods and Data Analysis:	Tumor response will be evaluated per RECIST 1.1 guidelines for all three tumor type cohorts. **Phase 1b:** Phase 1b is based on a 6+3 de-escalation design described in the Study Design Section. The primary objectives are to establish a RP2D or MTD and to evaluate safety and tolerability of ibrutinib in combination with MEDI4736. Adverse events (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, pharmacokinetics and pharmacodynamics in subjects receiving the combination regimen. Overall response rate (ORR), DCR at Week 20 (Cycle 5), and DOR will be calculated and summarized by tumor type and dose cohort descriptively. Pharmacokinetics and pharmacodynamics data will be evaluated by tumor type and dose cohort. **Phase 2:** Phase 2 will use the RP2D ascertained in Phase 1b. For the NSCLC and breast cancer cohorts, an interim analysis will be performed based on 18 evaluable subjects and the primary analysis will be performed based on 43 evaluable subjects per tumor type cohort. For the pancreatic cancer cohort, an interim analysis will be performed based on 17 evaluable subjects and the primary analysis will be performed based on 44 evaluable subjects. The primary analysis will be performed after all evaluable subjects have completed at least two response assessments or progressed prior to the second response assessment. For Phase 2, the following analyses will be undertaken: **Primary Efficacy Endpoint:** The primary efficacy endpoint is the ORR per RECIST 1.1 guidelines in each of the three solid tumor cohorts. The observed response rate along with its 95% confidence interval will be calculated for each tumor type cohort. **Secondary Efficacy Endpoints:** Disease control rate (DCR) at Week 20 (Cycle 5) will be calculated and its 95% confidence interval will be provided. Duration of response (DOR) will be calculated and summarized by 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. Progression-free survival (PFS) and OS will be evaluated by tumor type cohort with Kaplan-Meier estimates. Pharmacokinetics and pharmacodynamics profiles will be evaluated by tumor type cohort and overall. **Exploratory Efficacy Analysis:** Subgroup analysis: For each tumor type cohort, a subgroup analysis will be conducted to calculate the response rate and its 95% confidence interval

	based on PD-L1 expression (positive versus negative). For the NSCLC cohort, a subgroup analysis will also be conducted for subjects with adenocarcinoma versus squamous-cell carcinoma. For the breast cancer cohort, a subgroup analysis will also be conducted for subjects with HER2-positive versus triple-negative cancers. Other analyses: Other exploratory efficacy variables will be summarized descriptively and include the following: • Immune-cell subsets • Non-BTK-related pharmacodynamics (ie, EGFR, ITK) • Plasma chemokine/cytokine levels • Genes and/or proteins including PD-L1 (within the tumor or other collected specimens) associated with sensitivity or resistance to ibrutinib **Safety Analysis:** Adverse events (AEs), SAEs, laboratory data, vital signs, other relevant safety data and dosing data will be listed and summarized by tumor type cohort.
Sample Size Determination:	**Phase 1b:** 6-36 subjects for DLT assessment (6-9 subjects in up to 4 dose cohorts, regardless of tumor type) **Phase 2:** ~130 subjects, including 6-9 subjects treated at the RP2D in Phase 1b and with the tumor type as defined for Phase 2. **For NSCLC* and breast cancer**:** • **Interim analysis:** 18 subjects of each of the 2 tumor types = 36 total • **Primary analysis:** 43 subjects of each of the 2 tumor types = 86 total * For the NSCLC cohort, subjects with adenocarcinoma and squamous-cell carcinoma will be enrolled at an approximate 2:1 ratio (ie, at least 15 subjects with squamous-cell carcinoma will be enrolled). **For the breast cancer cohort, subjects with triple-negative and HER2-positive breast cancer will be enrolled at an approximate 2:1 ratio (ie, at least 15 subjects with triple-negative breast cancer will be enrolled). **For pancreatic cancer:** • **Interim analysis:** 17 subjects • **Primary analysis:** 44 subjects The Phase 2 portion will test a true response rate of 10% (H0) versus 25% (Ha) for the NSCLC and breast cancer cohorts and 5% (H0) versus 18% (Ha) for the pancreatic cancer cohort. The null hypothesis will be rejected if 8 or more responders are observed among the 43 evaluable subjects in the NSCLC and breast cancer cohorts. The null hypothesis will be rejected if 5 or more responders are observed among the 44 evaluable subjects in the pancreatic cancer cohort. With a 1-sided type I error rate of 0.05, each cohort would have 80% power based on the true response rate in the

	alternative hypothesis. The above statistical design including number of subjects and number of responders for each analysis follows the statistical framework of Simon's optimal 2-stage design (Simon, 1989). The enrollment will continue while the interim analysis is performed. The decision rule for consideration of discontinuation of each cohort at the interim analysis is described in the Study Design section above.

ABBREVIATIONS

AC	doxorubicin, cyclophosphamide
ADA	Anti-drug antibody
AE	adverse event
AESI	Adverse Events of Special Interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
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
CA19-9	carbohydrate antigen 19-9
CEA	carcinoembryonic antigen
CEF	cyclophosphamide, epirubicin, 5-fluorouracil
CLL	chronic lymphocytic leukemia
CMF	cyclophosphamide, methotrexate, 5-fluorouracil
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
Cys	Cysteine
DCR	disease control rate
DLRC	Dose Level Review Committee
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EC	epirubicin, cyclophosphamide
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ER	estrogen receptor
FAC/CAF	5-fluorouracil, doxorubicin cyclophosphamide
FCR	fludarabine/cyclophosphamide/rituximab
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded

GCP	Good Clinical Practice
GLP	good laboratory practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor family member 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
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
IHC	immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
ITK	interleukin-2-inducible kinase
IV	Intravenous
κ-Ras	Kirsten rat sarcoma viral oncogene homolog
LD	longest diameter
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NK	natural killer
NOAEL	no observed adverse effect level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	Overall survival
PCR	Polymerase Chain Reaction
PD	progressive disease
PD-L1	programmed death-ligand 1
PET	Positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	per os (oral)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time

Q2W	every 2 weeks
QTc	QT interval corrected for heart rate
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
REB	research ethics board
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
sPD-L1	soluble PD-L1
$t_{1/2}$	half-life
T-DM1	ado-trastuzumab emtansine or trastuzumab-DM1
Th	T-helper
TLS	tumor lysis syndrome
T_{max}	time to maximum plasma concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VEGFR-2	vascular endothelial growth factor receptor-2

1. BACKGROUND

1.1. Non-Small Cell Lung Cancer

Lung cancer is the leading cause of death due to cancer in the United States (US). In 2014, more than 110,000 new cases of lung and bronchial cancer in men and more than 100,000 new cases in women are expected to be diagnosed, and more than 150,000 deaths are estimated to occur due to lung cancer (Siegel 2014). The 5-year survival rate for lung cancer is 16.6% (Siegel 2014, Howlader 2009). Non-small cell lung cancer (NSCLC) accounts for 85-90% of all lung cancer cases and NSCLC includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLC is most commonly associated with smoking tobacco or exposure to tobacco smoke or other pollutants but can be seen in anyone. Treatment options include combinations of surgery, radiation therapy, chemotherapy and molecularly-targeted therapies (eg, epidermal growth factor receptor [EGFR], anaplastic lymphoma kinase [ALK], mitogen-activated protein kinases [MAPK], phosphatidylinositide 3-kinases [PI3K] and others) (National Comprehensive Cancer Network [NCCN] guidelines for NSCLC). Except for very early stage disease, treatment is generally not curative and therapy is used to prolong survival. The presence of EGFR mutations within the tumor strongly predicts an improved response rate and progression-free survival (PFS). EGFR-targeted agents and ALK-inhibitors have been approved for use in NSCLC.

Although many new active drugs and a multitude of chemotherapies in combination or as monotherapies are currently available for lung cancer, per NCCN guidelines, the reported second- and third-line response rates to systemic chemotherapy have generally been less than 10% underscoring that treatment of NSCLC remains an unmet medical need. Treatment for relapsed or refractory NSCLC is under investigation with EGFR- and additional targeted therapies in clinical trials. Patients with genetic alterations (eg, mutations in EGFR, the human epidermal growth factor receptor family member 2 [HER2], B-Raf proto-oncogene [BRAF], and Kirsten rat sarcoma viral oncogene homolog [KRAS]; ALK, ROS proto-oncogene 1 [ROS1] and RET gene re-arrangements; MET amplification; and others) for which a targeted agent are available may be treated differently from patients with an absence of mutation(s).

Thus, in the relapsed setting where patients are heavily pretreated, there remains a need for novel and improved therapies with improved safety profiles.

1.2. Breast Cancer

It is estimated that more than 235,000 patients in the US will be diagnosed with invasive breast cancer and more than 40,000 will die of the disease in 2014 (Siegel 2014). In 2013, more than 64,000 additional cases of in situ breast cancer were diagnosed (DeSantis 2014, NCCN guidelines for breast cancer). Breast cancer is the most common malignancy in women in the US. The incidence of breast cancer has increased over the past decades, potentially due to greater surveillance, but the breast cancer mortality appears to be declining (Early Breast Cancer Trialists' Collaborative Group [EBCTCG] 2005, Berry 2005), suggesting a benefit from screening and improved treatment (Berry 2005). Many risk factors have been identified: female

gender, genetic mutations, age, family history, early menarche, late menopause, giving birth late, hormone replacement therapy, chest wall irradiation, benign proliferative breast disease, and increased breast density. Proliferative abnormalities in breast tissue are usually limited to the lobular and ductal epithelium and include hyperplasia, in situ carcinoma, and invasive carcinoma (Dupont 1985). Invasive carcinomas are ductal in origin in approximately 85%–90% of cases (Dupont 1985). Invasive ductal carcinomas include mucinous, adenoid cystic, and tubular carcinomas, which have favorable natural histories. In addition, other biologic features of the tumor can contribute to staging of the disease, assessment of recurrence risk, and predicting response to therapy, eg, expression of estrogen receptor, progesterone receptor, and the HER family member 2 (HER2). Estrogen and progesterone receptor status is usually determined by immunohistochemistry (IHC). HER2 testing can be done by assessing HER2 cell-surface receptors by IHC or by in situ hybridization (Wang 2000, Wolff 2013, Wolff 2014). If more than 10% of tumor cells are HER2 positive by IHC or the average HER2 copy number is more than 6.0 per cell by in situ hybridization, the tumor sample is considered positive. DNA microarray techniques identifying a gene expression profile can also be used to profile tumors (Jeffrey 2005). Hormone receptor status (estrogen and progesterone receptor) and expression of HER2 have significant therapeutic implications in the treatment of this disease.

The clinical presentation is often asymptomatic and many cases are detected early in disease. Treatment of local breast cancer includes surgery, which may be curative in early stages, and radiation, or a combination of the two. Treatment of systemic breast cancer includes chemotherapy, endocrine therapy, and biologic therapy, or combinations of these. Adjuvant breast cancer therapy is used to treat lymph node disease or micrometastases. Selection of treatment is made based on prognostic and predictive factors, including tumor histology, clinical and pathological tumor characteristics, hormone receptor status, HER2 status, genetic testing, presence of metastatic disease, menopausal status, age, and comorbidities. Breast cancer may occur in men and treatment is similar to that of postmenopausal women except that when using aromatase inhibitors, testicular steroidogenesis needs to be suppressed (Giordano 2002a, Giordano 2002b). Per NCCN guidelines, breast cancer may further be divided into (1) noninvasive carcinomas, (2) locoregional invasive carcinoma with or without associated noninvasive carcinoma, (3) inoperable locoregional invasive carcinoma with or without associated noninvasive carcinoma, and (4) metastatic or recurrent carcinoma. In the past decade, many new and targeted therapies have been developed for the treatment of relapsed and metastatic breast cancer and have greatly improved overall survival. Many systemic therapies for breast cancer have an intolerable safety profile, eg frequently lead to hematologic side effects or neuropathy. Treatment options with a favorable safety profile for recurrent disease in a heavily pretreated patient population are still needed.

1.2.1. HER-2-positive Breast Cancer

HER2 over-expression is seen in approximately 15%-30% of invasive breast cancers and is associated with a more aggressive tumor phenotype and a worse prognosis. Patients with HER2-positive tumors can benefit from HER2-targeted therapies (Slamon 1989, Slamon 1987, Hudis 2007, Meric-Bernstam 2006, Giordano 2014, Mitri 2012). Treatment with HER2-targeted agents has been shown to improve survival for patients with early-stage or metastatic breast cancer (American Society of Clinical Oncology [ASCO]: Breast cancer. http://www.cancer.net/cancer-types/breastcancer; Gonzalez-Angulo 2009). The combination of pertuzumab, a HER-dimerization inhibitor, plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged PFS in the randomized, double-blind, multinational, phase III CLEOPATRA trial (Keating 2012). Median overall survival (OS) was 40.8 months in the placebo arm and 56.5 months in the pertuzumab arm, with a difference of 15.7 months (ESMO abstract 3500_PR 2014). Several new agents have been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic HER2-positive breast cancer since the approval of trastuzumab (Herceptin®) (Giordano 2014), but improvements for second and third line therapy are still needed because response rates and PFS in the relapsed setting are low, as expected, especially after multiple lines of prior therapy. In the EMILIA study (Verma 2012), 991 patients who were previously treated with trastuzumab and a taxane were randomly assigned to T-DM1 (ado-trastuzumab emtansine or trastuzumab-DM1 [KADCYLA®]) or lapatinib (TYKERB®) in combination with capecitabine (Xeloda®). Response rates were 42.6% for the patients who received T-DM1 and 30.3% for the patients who received lapatinib in combination with capecitabine. Median PFS for these patients were 9.6 months and 6.4 months, respectively. Rates of adverse events (AEs) of grade 3 or above were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%) (Verma 2012). In a smaller study with 66 patients, patients with metastatic HER2-positive breast cancer who had experienced progression during prior trastuzumab therapy received trastuzumab and pertuzumab and the response rate was 24.2% with a PFS of 18.5 months (Baselga 2010).

The reported response rate in third line is yet lower. In the GSK-EGF100151 study (Geyer 2006, Cameron 2010), patients with HER2-positive locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab were randomly assigned to receive either combination therapy with lapatinib and capecitabine or capecitabine monotherapy. The safety profile showed no increase in serious toxic effects with the combination (Geyer 2006). The response rate was 22% and 14% for the two treatment arms, respectively (Geyer 2006). In the THERESA study, 602 patients with progressive HER2-positive advanced breast cancer who had received two or more HER2-directed regimens were randomly assigned to T-DM1 or physician's choice (404 and 198 patients, respectively); 219 (54%) patients in the T-DM1 group and 129 (65%) of patients in the physician's choice group had PFS events after a median follow-up of 7.2 and 6.5 months, respectively. PFS was significantly improved with T-DM1 compared with physician's choice (median 6.2 months vs 3.3 months); a lower incidence of grade 3 or worse AEs was reported

with T-DM1 than with physician's choice (Krop 2014). Thus, since response rates and PFS times are relatively low in the relapsed setting, there remains a need for additional therapies, especially therapies with a tolerable safety profile for this heavily pretreated patient population.

1.2.2. Triple-negative Breast Cancer

Triple-negative breast cancer represents 10%–20% of invasive breast cancers (Boyle 2012) and is defined as estrogen receptor-negative, progesterone receptor-negative, and HER2-negative breast cancer. Triple-negative breast cancer is usually more aggressive compared to estrogen receptor-positive disease. Hormonal agents (eg, tamoxifen, aromatase inhibitors) that are commonly used in the treatment of breast cancer are ineffective, due to the absence of the corresponding receptors. Therapeutic options for patients with estrogen receptor-negative breast cancer are generally limited to a few chemotherapeutic agents.

Several regimens have been shown to be active in patients with advanced breast cancer. Among combination regimens, per NCCN, the panel includes FAC/CAF (5-fluorouracil, doxorubicin cyclophosphamide); CEF (cyclophosphamide, epirubicin, 5-fluorouracil); AC (doxorubicin, cyclophosphamide); EC (epirubicin, cyclophosphamide); CMF (cyclophosphamide, methotrexate, 5-fluorouracil); docetaxel, capecitabine; gemcitabine, paclitaxel; and paclitaxel, bevacizumab.

CAF has a response rate of 82 % versus 62% for CMF in a study where 78 patients with advanced metastatic breast cancer were randomized to either treatment. There was no significant difference in duration of response for the two arms (Bull 1978). In a study where 460 patients were randomized to either CEF or CMF, the overall response rate for CEF was with 57% higher than that for CMF with 46% (Ackland 2001). Time to progression was significantly longer with CEF compared to CMF (8.9 vs. 6.3 months with a 20-month follow-up time)(Ackland 2001). Response rates in a study comparing 105 patients who received FAC-BCG with 44 patients who received FAC alone were similar with 76% vs. 73%, however the duration of remission was longer (14 months vs. 9 months, respectively) and survival was significantly longer (24 months vs. 15 months, respectively) (Hortobagyi 1979).

These listed chemotherapy regimens are used in patients with triple-negative breast cancer. The use of platinum-based regimens has also been explored. In a Phase 2 study of patients with metastatic triple-negative breast cancer, the efficacy and safety of gemcitabine and carboplatin with or without iniparib, a small molecule with PARP-inhibitory activity, was tested. The overall response rate was 52% (n=32) for the combination with iniparib and 32% (n=20) without iniparib (O'Shaughnessy 2011a). PFS was 5.9 and 3.6 months, respectively. The most common AEs were neutropenia, anemia and thrombocytopenia (O'Shaughnessy 2011a). A phase 3 trial testing this combination did not meet the pre-specified criteria for significance for co-primary endpoints of OS and PFS (O'Shaughnessy 2011b). However, in the relapsed setting combination chemotherapy provides higher overall response rates without a significant improvement in survival relative to single-agent therapy. Therefore, for patients with comorbidities or patients

who do not have aggressive disease, single-agent treatments with a more favorable safety profile are warranted.

More recently, for patients with triple-negative relapsed and metastatic breast cancer who were enrolled in a Phase 3 study using ixabepilone (IXEMPRA®, an epothilone B analogue), in combination with capecitabine or capecitabine monotherapy, the response rates were 27% (n=91) for the combination and 9% (n=96) for capecitabine monotherapy (Pivot 2009). The median PFS was 4.1 months and 2.1 months, respectively. AEs were similar in patients with triple-negative breast cancer and the overall population; among the most frequent grade 3 or higher AEs were neutropenia, leucopenia and neuropathy (Pivot 2009). Another randomized Phase 3 study evaluated Halaven® (eribulin mesylate) versus capecitabine in 1,102 women with locally advanced or metastatic breast cancer who had up to 3 prior chemotherapy regimens. AEs were consistent with the known side-effect profiles of both drugs. For the subgroup with triple-negative breast cancer, the median OS was 14.4 months compared to 9.4 months on capecitabine (Study 301 presented at 2012 SABCS). Also, a recent randomized phase 3 study evaluating adjuvant bevacizumab (Avastin®)-containing therapy in triple-negative breast cancer (BEATRICE study) led to the conclusion that bevacizumab cannot be recommended as adjuvant treatment in unselected patients with triple-negative breast cancer; an exploratory biomarker assessment suggested that patients with high pre-treatment plasma VEGFR-2 (vascular endothelial growth factor receptor-2) might benefit from the addition of bevacizumab (Cameron 2013), but this is not considered standard practice.

In summary, several studies are underway attempting to improve the outcome in patients with triple-negative breast cancer, a subtype with limited treatment options beyond surgery, radiation and chemotherapy. The reported PFS for several agents is relatively short. The above data indicate that new agents and approaches are needed for this subset of patients.

1.3. Pancreatic Adenocarcinoma

During the year 2014 in the United States, more than 45,000 patients are estimated to be diagnosed with pancreatic cancer, and the majority of these patients are expected to die of their disease (Siegel 2014, NCCN guidelines for pancreatic cancer). After lung cancer, breast/prostate cancer, and colorectal cancer, pancreatic cancer is the fourth most common cause of death due to cancer in the US (Siegel 2014). The peak incidence of pancreatic cancer is in the seventh and eighth decade of life (Siegel 2014), and pancreatic cancer is thought to be more common in African Americans (Arnold 2009). The incidence of pancreatic cancer in the US recently increased, most likely due to the obesity epidemic, an aging population, and other unknown factors (Simard 2012, Eheman 2012, Smith 2009). Among the risk factors for pancreatic cancer are a genetic predisposition, increased body mass index (BMI) (Alsamarrai 2014, Larsson 2007, Li 2009, Patel2009), chronic pancreatitis, cigarette smoking (Anderson 2012), as well as red meat (Larsson 2005) and alcohol consumption (Lucenteforte 2012).

The best validated and most clinically used biomarker in pancreatic cancer is carbohydrate antigen (CA) 19-9, which is not tumor-specific, however has potential use in diagnosis, screening, staging, determining resectability, as a prognostic marker after surgery and as a predictive marker for response to chemotherapy (Morris-Stiff 2012). CA 19-9 is a poor biomarker for screening due to a low positive predictive value, but a good diagnostic marker with a sensitivity and also specificity of more than 80% (Ballehaninna 2012). A recent study found that normalization of CA 19-9 was associated with improved overall survival in 141 patients with pancreatic cancer who were treated with chemotherapy, and this was the case in those who had surgery and in those who were treated conservatively (Tzeng 2014).

Therapies for pancreatic adenocarcinoma include surgery, radiation, chemotherapy, and targeted therapies. The only curative treatment (although rare) is resection, with the best outcome as expected in early stages of the disease. In regards to chemotherapy, the response rate for pancreatic adenocarcinoma first-line treatment is approximately 20-30% (ORR 23% in Von Hoff 2013, Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine; ORR 19.1% in Cunningham 2009, Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer; ORR >30% in the ACCORD trial, Randomized phase II trial comparing folfirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA) (Ychou 2007). For second-line treatment with a single agent, the reported response rate is lower and ranges between 0% and 15% in different clinical trials (Walker 2014). For other second-line treatments with single-agent and combination regimens, the response rates vary between 0% and 30% in different clinical trials (Rahma 2013, Walker 2014), with the majority of trials having a response rate below 10% (Rahma 2013, Walker 2014). Thus, new treatment options are needed for advanced pancreatic cancer, especially treatment options with a tolerable safety profile for this usually very ill patient population.

1.4. Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered covalentlybinding inhibitor of Bruton's tyrosine kinase (BTK) by Pharmacyclics LLC for the treatment of B-cell malignancies. Ibrutinib has been approved in many regions, including the US and EU, for indications covering the treatment of patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, first-line treatment of patients with CLL with a deletion of the short arm of chromosome 17 (del17p) or a *TP53* mutation, and patients with Waldenström's Macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

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 B-cell receptor (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).

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 (ibrutinib IB).

1.4.1. Summary of Nonclinical Data

1.4.1.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk (Pan 2007). *In vitro*, ibrutinib is a potent inhibitor of Btk activity (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 BCR and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

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

1.4.1.2. Safety Pharmacology and Toxicology

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 studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current ibrutinib IB.

1.4.2. Summary of Clinical Data

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

1.4.2.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally to doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most comprehensive pharmacokinetics (PK) and product metabolism, please refer to the current version of the ibrutinib IB.

1.4.3. Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided below. For more comprehensive safety information please refer to the current version of the ibrutinib IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

1.4.3.1. Monotherapy Studies in Hematologic Malignancies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

1.4.3.2. Combination Studies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

1.4.4. Risks

1.4.4.1. Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.2.3 for guidance

on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

1.4.4.2. Atrial fibrillation

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. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.5.1.4)

1.4.4.3. Cytopenias

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

1.4.4.4. Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events were rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.5.1.4).

1.4.4.5. 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 NCI Common Terminology Criteria for Adverse Events (CTCAE, v4.03). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

1.4.4.6. Other Malignancies

Other malignancies, most frequently skin cancers, have occurred in subjects treated with ibrutinib. Other malignancies including non-skin carcinomas have occurred in patients treated with ibrutinib. The most frequent second primary malignancy was non-melanoma skin cancer.

1.4.4.7. 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.

1.4.4.8. 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 TLS are those with comorbidities and risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities**.**

1.4.5. Summary of Clinical Data

This is an exploratory study and there is no clinical data on the use of the combination of ibrutinib and MEDI4736 in NSCLC (adenocarcinoma and squamous-cell carcinoma), HER2-positive breast cancer, triple-negative breast cancer or pancreatic adenocarcinoma.

1.5. Durvalumab (MEDI4736) Overview

AstraZeneca and MedImmune are pursuing development of durvalumab (MEDI4736) as a potential anticancer therapy for patients with advanced solid tumors. 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], cluster of differentiation [CD]274) 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).

1.5.1. 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/PD and potential toxicity of MEDI4736. Following intravenous (IV) administration, the PK of

MEDI4736 in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and $t_{1/2}$ increased with increasing doses, suggesting saturable target binding-mediated clearance of MEDI4736. No apparent gender differences in pharmacokinetics 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) pharmacokinetics and pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with anti-drug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, pharmacokinetics and 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)

1.5.2. Summary of Clinical Data

Clinical experience with durvalumab (MEDI4736) is fully described in the current version of the durvalumab Investigator's Brochure (Version 8.0).

As of the data cut off dates (15Apr2015 to 12Jul2015, Durvalumab IB Version 8.0), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

Pharmacokinetics and Product Metabolism

Study CD-ON-durvalumab-1108: As of 09 Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. 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 3 mg/kg and increased dose-proportionally at ≥3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses <3 mg/kg and approaches linearity at doses ≥3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, >90% of subjects are expected to maintain PK exposure ≥40 μg/mL throughout the dosing interval.

As of 09 Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

1.5.3. Summary of Clinical Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below.

Adverse Event Profile of durvalumab Monotherapy

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the

case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07 May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with Grade ≥3 events occurring in 65 subjects (9.4%). Treatment-related Grade ≥3 events reported in 3 or more subjects (≥0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were Grade ≥3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were Grade ≥3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception

of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

1.5.4. Summary of Clinical Efficacy

Study CD-ON-durvalumab-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥24 weeks follow-up, measurable disease at baseline, and ≥1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease (SD) in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-durvalumab-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥12 weeks) was 79.4%.

1.6. Study Rationale

With respect to MEDI4736, PD-L1 expressed on tumor cells inhibits anti-tumor immune responses (Zou 2008). PD-1 is expressed on activated T cells, B cells and myeloid cells to

modulate immune activation or inhibition (Butte 2008). MEDI4736 is a PD-L1 inhibitor which binds to PD-L1 and allows T cells to recognize and kill tumor cells (MedImmune/AstraZeneca, Data on file). Preclinical and early clinical data suggest a benefit with PD-L1 inhibitors for patients with NSCLC and pancreatic adenocarcinoma. Preclinical data suggests a benefit in HER2-positive breast cancer models. PD-L1 is often expressed in triple-negative breast cancer, and patients with triple-negative breast cancer are currently enrolled in a trial with a PD-L1 inhibitor at MedImmune/AstraZeneca (efficacy data are pending).

With respect to the anti-tumor activity of ibrutinib, there are three potential mechanisms that may be operative in solid tumors: (1) direct tumor effects, eg inhibition of EGFR, HER2; (2) changes in the tumor microenvironment, eg inhibition of mast cell function; and (3) changes in immune profiles, eg alteration of Th1/Th2 polarity.

With these distinct mechanisms of action, MEDI4736 and ibrutinib may act synergistically in enhancing the host anti-tumor response.

The effects of the combination of an anti–PD-L1 antibody and ibrutinib in suppressing tumor growth were documented in mouse models of a variety of solid tumors, such as triple negative breast cancer. The enhanced therapeutic activity of PD-L1 blockade by ibrutinib was accompanied by enhanced antitumor T-cell immune responses. These preclinical results suggest that the combination of PD1/PD1-L blockade and ibrutinib should be tested in the clinic (Sagiv-Barfi 2015).

1.6.1. MEDI4736

1.6.1.1. Tumor Immunotherapy and Programmed Death-Ligand 1 (PD-L1)

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked by the host immune system. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. PD-L1 is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some indications. In a number of these cancers, including lung (Mu 2011), renal (Thompson 2005; Thompson 2006; Krambeck 2007), pancreatic (Nomi 2007; Loos 2008; Wang 2010), and ovarian cancer (Hamanishi 2007), tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. For example, in ovarian cancer, the 5-year survival rate in patients with low expression of PD-L1 was 80.2% compared to 52.6% in patients with high expression levels of PD-L1 (Hamanishi 2007). In lung cancer, only 20% of patients with tumors expressing PD-L1 survived for more than 3 years compared to 49% of patients with tumors lacking PD-L1 expression (Mu 2011). Along with PD-L1 expression data generated at MedImmune/AstraZeneca, these data suggest that an antibody targeting PD-L1 may have the potential to affect multiple solid tumor types.

Programmed death-ligand 1 (PD-L1) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses 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 PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir 2008, Park 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells that are reaching the tumor. The binding delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou 2008).

Ten clinical studies of MEDI4736 are ongoing (5 employing MEDI4736 as monotherapy and 5 as combination therapy) across various tumor indications. Encouraging clinical activity of MEDI4736 combined with acceptable and manageable safety has been demonstrated across the monotherapy and combination therapy studies. These data provide a sound rationale for further development of MEDI4736 in advanced solid tumors and hematologic malignancies (MEDI4736 IB).

1.6.2. Ibrutinib

1.6.2.1. Direct Tumor Effects-ErbB Family Kinase Inhibition by Ibrutinib

Ibrutinib binds covalently to the Cystein-481 residue which is within the active site of BTK. Since this residue is conserved in only 9 other kinases, such binding affords a high degree of selectivity with once daily dosing. The ErbB family of kinases are, however, among those retaining homology, and the ability of ibrutinib to target these kinases in tumors has been studied (Elias 2013, Chen 2014). Significant *in vitro* growth inhibitory activity of ibrutinib at concentrations within those attainable clinically was demonstrated in HER2-amplified breast cancer lines. Growth inhibition was further demonstrated *in vivo* in a mouse xenograft model at clinically relevant doses. Importantly, the anti-tumor activity of ibrutinib in HER2-positive breast cancer cell lines was superior to that of lapatinib, which is approved for this indication, and its enzymatic potency for HER2 (measured by IC_{50}) was nearly three times lower.

Ibrutinib was also found to have anti-tumor activity in a panel of EGFR-driven NSCLC cell lines (Gao 2014). Three cell lines were highly susceptible to ibrutinib, with IC_{50} between 0.002 and 0.195 uM. Two of the cell lines tested (including erlotinib-resistant H1975 cells) harbored activating mutations in the EGFR gene. Ibrutinib was found to selectively inhibit growth of cells carrying these mutations. Importantly, the H1975 cell line was insensitive to erlotinib, but susceptible to ibrutinib. The effect of ibrutinib on EGFR-phosphorylation was also analyzed. Ibrutinib induced dose-dependent inhibition of phosphor-EGFR at both Y1068 and Y1173 sites, suggesting ibrutinib functions as an EGFR inhibitor (Gao 2014). The expression of BTK was not detectable in all cell lines tested, indicating that ibrutinib-induced antitumor activity in these cells was not mediated by BTK. An *in vivo* study showed that ibrutinib suppressed H1975 tumor cell growth and prolonged survival of the tumor-bearing mice. These results indicate that ibrutinib

could be a candidate drug for treatment of EGFR-mutant NSCLC, including erlotinib-resistant tumors (Gao 2014). Further, ibrutinib exhibited superior *in vitro* growth inhibition to erlotinib in a patient-derived xenograft bearing the L858R/T790M mutation and had nearly twice the potency compared to gefitinib against this mutant EGFR in enzyme-activity assays.

1.6.2.2. BTK-mediated Microenvironment Modulation

Several emerging lines of evidence suggest that BTK inhibition in solid tumors may be relevant due to modulation of the tumor microenvironment. These mechanisms may be applicable for a wide range of solid tumor types. Ibrutinib has been shown to inhibit *in vivo* tumor growth in a myc-driven genetically engineered pancreatic islet cell carcinoma model, and more recently in a k-ras driven pancreatic ductal adenocarcinoma model. This was attributed in both models to inhibition of mast-cell degranulation with a resulting anti-angiogenic effect (Soucek 2011, Masso-Valles 2013, Masso-Valles 2015). Extensive correlative evidence points to a role of infiltrating mast cells in progression of numerous tumor types (Dalton 2012), as does direct functional evidence from genetically engineered models (Soucek 2007, Chang 2011, Ma 2013). Bruton tyrosine kinase (BTK) is known to be essential for IgE-stimulated basophile degranulation (Iwaki 2005), a function which has been shown to be inhibited by ibrutinib (MacGlashan 2011), and which was also inhibited in mast-cell models (Soucek 2011, Masso 2013). Ibrutinib treatment in these reports was also associated with decreases of Gr1+ infiltrating myelomonocytic cells which may contribute pro-angiogenic and pro-proliferative signaling. All described mechanisms may contribute to an anti-tumor effect.

1.6.2.3. ITK (Interleukin-2-inducible Kinase)-mediated T-Cell Polarization

Ibrutinib is an irreversible inhibitor of interleukin-2-inducible kinase (ITK) (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. Patients with CLL treated with ibrutinib have been shown to have shifts of T-helper (Th) polarization to a more favorable Th1 bias (Dubovsky 2013). In addition, studies of T-cell function *in vitro* and in murine neoplastic (CLL), parasitic infection (Leishmania major), and infectious disease (Listeria monocytogenes) models *in vivo*, analyses have confirmed ibrutinib as a clinically relevant and physiologically potent ITK inhibitor (Dubovsky 2013). ITK inhibition reduces Th2-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 checkpoint inhibitors such as PD-L1-inhibitors.

1.7. Study Rationale in Specific Solid Tumors

1.7.1. Non-small Cell Lung Cancer (NSCLC)

The role of EGFR inhibition in lung cancer is well established. Responsiveness correlates primarily to the presence of EGFR activating mutations, with resistance often correlating with

development of the gatekeeper mutation T790M, and activation of other pathways involving MET or k-RAS, for example. Nonetheless patients progressing on (or not tolerating) one EGFR inhibitor may subsequently respond to another inhibitor (Wong 2010, Teng 2014, Watanabe 2011). Importantly, ibrutinib has been found to have anti-tumor activity in both EGFR wild-type and mutant NSCLC cell lines. NSCLC is also being recognized as potentially more sensitive to immunologic mechanisms than has been suggested in the past, and evidence has suggested a role for mast cells in NSCLC progression (Takanami 2000, Ullah 2012). Therefore, the ability of ibrutinib to modulate T-cell subsets and mast cell activation could be relevant and ibrutinib may act synergistically with the ability of MEDI4736 to stimulate T-cell activity and augment its established clinical activity in NSCLC.

With MEDI4736, in multiple tumor types including NSCLC, early and durable clinical activity (tumor reduction) was observed at multiple doses as early as 6 weeks, and was maintained through 67+ weeks and off active therapy (Lutzky 2014). Phase 3 studies in NSCLC using the dose of 10 mg/kg every 2 weeks for 12 months are underway.

1.7.2. Breast Cancer

In *in vivo* breast cancer models, ibrutinib was shown to sensitize 4T1 mammary tumor cells to anti-PD-L1 treatment with respect to inhibition of tumor cell growth (Sagiv-Barfi et al, unpublished results). Treatment with ibrutinib and a PD-L1 inhibitor was also effective in suppressing lung metastasis (Sagiv-Barfi et al, unpublished results).

In light of the encouraging preclinical data showing that ibrutinib in combination with a PD-L1 inhibitor is effective in breast cancer models, testing the combination of ibrutinib and MEDI4736 in patients with specific subtypes of metastatic breast cancer is warranted.

1.7.2.1. HER2-positive Breast Cancer

HER2-expressing breast cancer is a well-recognized indication for HER2-targeted therapy, with multiple tyrosine-kinase inhibitors and monoclonal antibodies approved and in use in this setting (Jelovac 2013). Further, response to re-treatment with similarly targeted HER2-antagonists after progression does indeed occur. For example, in the EMILIA study (Verma 2012), 991 patients who were previously treated with trastuzumab and a taxane were randomly assigned to T-DM1 (ado-trastuzumab emtansine or trastuzumab-DM1 [KADCYLA®]) or lapatinib (TYKERB®) in combination with capecitabine (Xeloda®). The overall survival was 30.9 months for the patients who received T-DM1 and 25.1 months for the patients who received lapatinib in combination with capecitabine. The response rates were 43.6% for T-DM1 and 30.8% for the combination. In a smaller study (Cortes 2012), 29 patients with HER2-positive breast cancer who failed prior trastuzumab (Herceptin®)-based therapy received pertuzumab and 17 patients continued to receive pertuzumab with the addition of trastuzumab. Although pertuzumab showed some activity in patients with HER2-positive breast cancer who failed prior trastuzumab-based therapy, the combination of pertuzumab and trastuzumab led to a PFS benefit (17.4 versus

7.1 weeks without trastuzumab). The response rates were 17.6% for the combination of pertuzumab and trastuzumab and 3.4% for pertuzumab monotherapy.

Another HER2 antagonist, TYKERB® (lapatinib), is used in combination with Xeloda® (capecitabine) for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2, and who have received prior therapy including an anthracycline, a taxane, and trastuzumab (TYKERB label). Ibrutinib was shown to have a level of enzymatic and cellular potency which appears to be at least comparable to that of lapatinib (Elias 2013, Chen 2014), and clinical testing of this indication is therefore of interest. When comparing ibrutinib to other ErbB inhibitors in breast-cancer cell lines, it was shown that breast cancer growth inhibition with ibrutinib was comparable to lapatinib, neratinib, dacomitinib, and afatinib in BT-474 and SK-BR3 cell lines (Chen 2014). Supported by the findings from the *in vivo* breast cancer models showing that ibrutinib has the potential to augment the activity of a PD-L1 antagonist such as MEDI4736, HER2-positive breast cancer seems an appealing target for the combination.

1.7.2.2. Triple-Negative Breast Cancer

There is evidence that triple negative breast cancer tumors express PD-L1. In a recent study, tumor biopsies from triple negative breast cancer patients with early and advanced metastatic disease who underwent primary surgery and distant lesion biopsy were examined for PD-L1 expression (Tessari 2014). PD-L1 was expressed in 100% of early triple negative breast cancer and in 92% of corresponding metastatic lesions. Another study using archived tumor samples also looked at PD-L1 expression in triple negative breast cancer (Mittendorf 2013). RNA sequencing showed greater expression of the PD-L1 gene in triple negative breast cancer versus non-triple negative breast cancer ($P < 0.001$). Further, PD-L1 positive tumors had greater CD8+ T-cell infiltrates than PD-1 negative tumors (688 cells/mm vs. 263 cells/mm; $P < 0.0001$) (Mittendorf 2013). Therefore, the combination of ibrutinib and MEDI4736 seems well suited for this subtype of breast cancer that has limited effective therapy options beyond standard chemotherapy.

1.7.3. Pancreatic Adenocarcinoma

Mast cells have previously been proposed as targets for cancer therapy (Soucek 2007). Soucek et al have shown that the oncogene *myc* can instruct a complex inflammatory program involving recruitment of mast cells, which are necessary in the tumor microenvironment for the physical expansion and maintenance of tumors. In a mouse pancreatic ductal adenocarcinoma model comprised of transgenic animals with pancreas-specific expression of κ-Ras^{G12D} (Hingorani 2003), which is one of the most common mutations in pancreatic cancer, it was shown that inflammatory cells including mast cells are present in the tumor microenvironment. With ibrutinib treatment, general tumor size was reduced (Soucek 2012). BTK is required for mast cell degranulation and when given in approved doses, ibrutinib achieves nearly complete BTK occupancy for 24 hours. In the model, mast cells are still recruited to the tumor microenvironment, but are no longer degranulating (Soucek 2012). Further, ibrutinib was shown

to reduce tumor proliferation and tumor vasculature (Soucek 2012). Ibrutinib also reduced inflammatory cell infiltration and reduced collagen deposition. Mice that were treated with ibrutinib had a survival benefit (Soucek 2012; Masso-Valles 2015).

The fact that pancreatic cancer has a dismal prognosis is in part related to its relative resistance to chemotherapy. New approaches are needed to treat this difficult disease. As reported by Segal et al (Segal 2014), MEDI4736 was shown to have early evidence of antitumor activity in pancreatic cancer patients. With the effect of ibrutinib on mast cells and other cells in the tumor microenvironment and the potential to augment the antitumor activity of MEDI4736, this novel combination provides a potential alternative approach to standard therapy for this disease.

1.8. Dosing Rationale

1.8.1. Ibrutinib Dose

Ibrutinib has been FDA-approved for MCL at a dose of 560 mg and for CLL at a dose of 420 mg. 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). 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). With respect to safety, 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 this data, fixed dose levels of >280 mg are expected to be necessary to ensure achievement of the full pharmacodynamics effect in the vast majority of patients. The sustained pharmacodynamics effect despite a relative rapid elimination of ibrutinib is secondary to irreversible inhibition of BTK in subjects' PBMCs (ibrutinib IB). Consistent with this, once-a-day oral dosing resulted in 24-hour sustained target inhibition in these trials.

In contrast to studies in B-cell malignancies, there are multiple possible enzymatic targets whose inhibition could contribute to efficacy in solid tumors. *In vitro* and preclinical studies have shown that ibrutinib covalently binds to the cysteine-481 amino acid of the BTK enzyme and inhibits numerous processes, including ERK signaling, NF-κB DNA binding, cytosine–phosphate–guanine (CpG)-mediated CLL-cell proliferation, and tumor-cell migration (ibrutinib IB). For solid tumors, the key target for mast cells and infiltrating myelomonocytic cells in the tumor microenvironment is BTK, whose inhibition can be reliably achieved at well tolerated doses. In addition, a high level of occupancy of the T-cell specific kinase ITK has been achieved in a study with CLL patients using ibrutinib doses of 420 mg once daily. The enzymatic IC_{50} of ibrutinib for EGFR and HER2 are higher than that for BTK, however the concentrations required for enzymatic inhibition in cells, and inhibition of cellular growth of sensitive cell lines *in vitro*, is similar to or only slightly higher than that required for BTK (Elias 2013; Chen 2014).

Growth inhibition of a breast cancer xenograft *in vivo* has furthermore been noted with doses that are effective, but not fully optimal, for BTK occupancy or for *in vivo* inhibition of lymphoma xenografts. Therefore, the approved doses of 560 or 420 mg/day may be effective in suppressing growth of tumors that are driven by ErbB receptors (epidermal growth factor receptor [EGFR; ErbB1], HER-2 [ErbB2], ErbB3, and ErbB4) (Yarden 2001, Olayioye 2000).

Due to the extensive clinical experience with the 560 mg dose in terms of safety and efficacy, and due to the expected variability in the sensitivity of the solid tumors studied in this trial, a dose of 560 mg/day has been chosen for the initial cohort in this study.

1.8.2. Durvalumab (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). The MEDI4736 10 mg/kg every-2-week cohort comprised subjects with nonsquamous NSCLC (n = 100), squamous NSCLC (n = 72), hepatocellular carcinoma (n = 20), triple-negative breast cancer (n = 26), pancreatic adenocarcinoma (n = 32), gastroesophageal cancer (n = 36), advanced cutaneous melanoma (n = 21), uveal melanoma (n = 23), squamous cell carcinoma of the head and neck (SCCHN, n = 59), and other (n = 4). 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. Treatment-related AEs (all grades) in >5% of subjects included fatigue (13.5%), nausea (8.4%), and diarrhea, rash, and decreased appetite (5.3% each). In general, Grade 3 or higher AEs were manageable with standard clinical toxicity management. Grade 3 or higher AEs that occurred in >1% of subjects were dyspnea (5.1%), increased gamma-glutamyltransferase (3.3%), fatigue, general physical health deterioration, increased aspartate aminotransferase, and back pain (2.3% each), anemia and dehydration (1.8% each), and abdominal pain, vomiting, sepsis, syncope, and hypotension (1.3% each). 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).

As reported at ASCO by Lutzky et al, in multiple tumor types including NSCLC, pancreatic cancer and triple-negative breast cancer relevant for this study protocol, 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 safety and efficacy data above, a dose of 10 mg/kg every 2 weeks for 12 months was chosen for the initial cohort in this study.

1.8.3. Ibrutinib and MEDI4736 in Combination

Based on the above findings which describe the safety and pharmacokinetics 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 26). 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 OBJECTIVE

2.1. Primary Objective

Phase 1b:

- To determine the Recommended Phase 2 Dose (RP2D) or MTD of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors
- To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors

Phase 2:

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

2.2. Secondary Objective(s)

Phase 1b:

- To evaluate the efficacy of ibrutinib in combination with MEDI4736 by assessing the ORR in subjects with relapsed or refractory solid tumors
- To evaluate the efficacy of ibrutinib in combination with MEDI4736 by assessing the DCR at Week 20 (Cycle 5)

- To evaluate the efficacy of ibrutinib in combination with MEDI4736 by assessing the DOR
- To determine the pharmacokinetics and pharmacodynamics of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors

Phase 2:

- To determine the efficacy of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors by assessing the DCR at Week 20 (Cycle 5), DOR, PFS, and OS
- To determine the safety and tolerability of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors
- To determine the pharmacokinetics and pharmacodynamics of ibrutinib in combination with MEDI4736 in subjects with relapsed or refractory solid tumors

2.3. Exploratory Objective(s)

- To evaluate immune-cell subsets after treatment with ibrutinib in combination with MEDI4736
- To evaluate non-BTK-related pharmacodynamics (ie, ITK, EGFR) 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/or proteins (within the tumor or other collected specimens) associated with sensitivity or resistance to ibrutinib and/or MEDI4736 (ie, PD-L1)

3. STUDY DESIGN

3.1. Overview of Study Design

This is a Phase 1b/2, multi-center study to assess the safety and efficacy of ibrutinib and MEDI4736 in subjects with relapsed or refractory solid tumors. A 6+3 de-escalation design will be employed in Phase 1b (see Section 5.2) to assess doses of ibrutinib in combination with MEDI4736 to determine the RP2D or MTD for this study. In Phase 2, independent analyses will be performed for each tumor type cohort to evaluate the response and safety profile of the combination therapy.

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 and will include a sentinel subject which will have a 3-day observation period prior to dosing of

subsequent subjects. Subjects with one of the following three tumor types will be eligible for enrollment:

- NSCLC (adenocarcinoma or squamous-cell carcinoma)
- Breast cancer (HER2 positive or triple negative)
- Pancreatic cancer (adenocarcinoma)

In cohort 1, 6 subjects regardless of tumor type, ibrutinib will be administered PO at a dose of 560 mg daily in combination with MEDI4736 at a dose of 10 mg/kg IV every 2 weeks in 28-day cycles until DLT or disease progression occurs. Re-treatment with MEDI4736 will not be permitted following completion of 12 months of therapy, regardless of any dose delays, missed doses, or following permanent discontinuation for any reason. Dosing of ibrutinib will continue for 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. The DLT observation period includes Cycle 1 and laboratory assessments on Day 1 of Cycle 2 which will occur before the MEDI4736 infusion on Day 1 of Cycle 2. 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 subjects experience a DLT, dose de-escalation will occur. If subject incidence of DLTs during the first 28 days (Cycle 1=28 days and including laboratory assessments on Day 1 Cycle 2) of study treatment 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.

A similar 6+3 cohort design will be utilized in the dose de-escalation cohorts (see Table 1 and Section 5.2). De-escalation cohorts -(minus)1A and -1B will be opened simultaneously to determine which dosing schedule is most appropriate for the phase 2 portion of the study. Determination of the RP2D will be based on the safety profile of the 2 treatment regimens. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter.

Table 1. 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 Cycle 1 Day 1.
b. MEDI4736 will be administered IV on Day 1 and Day 15 of each 28-day cycle for a maximum of 12 months.
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 5.3.

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.

Phase 2:

Subjects with one of three solid tumor types (Stage III/IV) will be enrolled in separate cohorts in the Phase 2 portion of this protocol:

- NSCLC (adenocarcinoma and squamous-cell carcinoma at an approximate 2:1 ratio)
- Breast cancer (triple-negative and HER2-positive breast cancer at an approximate 2:1 ratio)
- Pancreatic cancer (adenocarcinoma)

For each of the above three cohorts, an interim analysis will be performed to evaluate the response and the safety profile. A cohort may be discontinued based on the interim efficacy and/or safety results. The decisions based on the results of the interim analysis are independent in the 3 individual disease cohorts.

At the time of the interim safety assessment, the safety team will review and make recommendations for the conduct of the study. Members of the safety team will include participating investigators or designees as well as the Sponsor (at a minimum: the Medical Monitor or designee, a Drug Safety representative and a Biostatistician). The safety team may recommend continuing the trial unchanged, or may recommend to consider modifying in part or in whole, or to stop the trial due to safety concerns.

NSCLC and breast cancer:

- **Interim analysis:** n=18 per tumor type
- **Primary analysis:** n=43 per tumor type

The NSCLC and breast cancer cohorts will enroll 18 subjects per tumor type for the interim analysis and additional 25 subjects per tumor type for the primary analysis (total n=43). An interim analysis will be performed after 18 subjects are evaluable for tumor response. If a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject will be replaced. If 2 or fewer responders are observed among the 18 evaluable subjects in a cohort, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment for responders) or tumor measurements (showing clinically relevant tumor reductions, ie, <30%, that fit the criteria for SD) may support continued enrollment.

Pancreatic cancer:

- **Interim analysis:** n=17
- **Primary analysis:** n=44

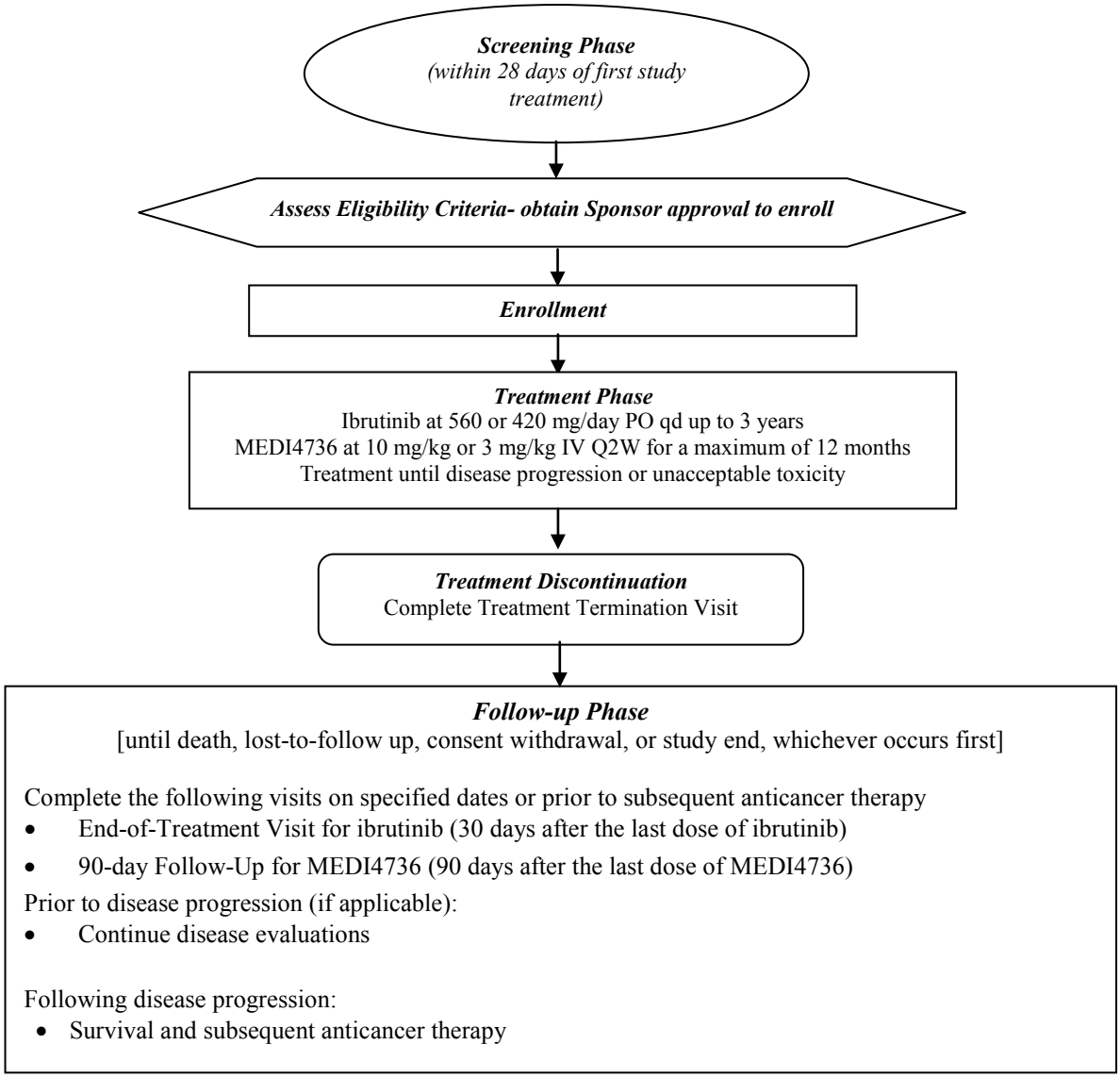
For the interim analysis, 17 subjects will be enrolled, and additional 27 subjects will be enrolled for the primary analysis (total n=44). An interim analysis will be performed after 17 subjects are evaluable for tumor response. If a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject will be replaced. If 1 or no responder is observed among the 17 evaluable subjects, the Sponsor may consider discontinuation of this cohort; however, assessment of biomarkers (that may aid in prospective enrichment for responders) or tumor measurements (showing clinically relevant tumor reductions, ie, <30%, that fit the criteria for SD) may support continued enrollment.

Subjects will receive ibrutinib (daily) and MEDI4736 (every 2 weeks) continuously in 28-day cycles until progressive disease or unacceptable toxicity. Dosing of MEDI4736 will continue for a total of 12 months (from initial dose) of therapy if clinical benefit is seen without safety concerns. Re-treatment with MEDI4736 will not be permitted following completion of 12 months of therapy, regardless of any dose delays, missed doses, or following permanent discontinuation for any reason.

Assessment for response will occur at the end of Cycle 2 (Cycle 2 Day 28 [–7 days]) and then after every 3rd cycle (Cycle x Day 28 [–7 days]). Assessments will include CT/MRI scans or physical examination (if the lesion is not assessable by CT/MRI) for the relevant tumor type (ie, superficial soft tissue lesions, skin lesions, etc.) and will follow RECIST 1.1 guidelines.

In order to accommodate the potential for immune flare (pseudoprogression), treatment with ibrutinib and MEDI4736 may continue between the initial assessment of suspected progression and confirmation of progression. Subjects with suspected progressive disease who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive ibrutinib and MEDI4736 as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion. In the absence of symptomatic deterioration, a biopsy (if lesion is assessable) should be performed at the time of suspected tumor flare (in order to rule out tumor necrosis and/or an inflammatory reaction) or the investigator may continue dosing and a CT /MRI scan or physical examination (if the lesion is not assessable by CT/MRI) should 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 met. Ibrutinib and MEDI4736 should be discontinued if there is confirmed progressive disease per RECIST 1.1 guidelines or other clinical data suggest clear evidence of progression (symptomatic deterioration).

3.1.1. 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. Pathologically confirmed:
   - NSCLC (adenocarcinoma or squamous-cell carcinoma) or
   - Breast cancer (HER2 positive [by FISH or IHC. See Section 1.2 for definition] or triple negative) or
   - Pancreatic cancer (adenocarcinoma)

2. For Phase 2 only: Provision of a fresh tumor biopsy or an available archival tumor sample processed as formalin-fixed paraffin embedded (FFPE) taken within 3 months, and after the most recent treatment with the following exception:
   - For locally advanced pancreatic cancer, a fresh biopsy is not required if the tumor is inaccessible or the procedure places the subject at a safety risk.
   - No more than 10 subjects with locally advanced pancreatic cancer will be enrolled in the study without a biopsy.
3. Radiographically or clinically documented relapsed or refractory disease (Stage III or IV): Subjects with NSCLC or pancreatic cancer must have relapsed or refractory disease and must have failed at least 1 prior appropriate systemic first-line treatment regimen. Subjects with epidermal growth factor receptor (EGFR) mutation-positive NSCLC must have received an EGFR inhibitor and subjects with NSCLC that is anaplastic lymphoma kinase (ALK)-positive must have received an ALK inhibitor. Subjects with breast cancer must have relapsed or refractory disease and must have failed at least 2 prior appropriate systemic regimens.
4. One or more disease lesion on CT/MRI scan or by physical examination (if the lesion is not assessable by CT/MRI) that is measurable (ie, superficial soft tissue lesions, skin lesions, etc.) per RECIST 1.1 guidelines.
5. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoetin which require discontinuation at least 14 days prior to screening defined as:
   - Absolute neutrophil count (ANC) >1500 cells/mm^3 (1.50 x 10^9/L)
   - Platelet count >100,000 cells/mm^3 (100 x 10^9/L)
   - Hemoglobin >9.0 g/dL
6. Adequate hepatic and renal function defined as:
   - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN) for subjects without liver metastases and ≤3.5 x ULN for subjects with liver metastases
   - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
   - Creatinine ≤2.0 x ULN and Creatinine Clearance ≥40 mL/min (Cockcroft-Gault or 24-hour creatinine clearance collection)
7. Prothrombin time (PT)/International normalized ratio (INR) <1.5 x upper limit of normal (ULN) and partial thromboplastin time (PTT)/ activated partial thromboplastin time (aPTT) <1.5 x ULN
8. Men and women ≥18 years of age
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; OR history of hysterectomy; OR history of bilateral

tubal ligation; OR history of bilateral oophorectomy). Female subjects of reproductive potential must have a negative serum pregnancy test upon study entry.

11. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug (see Appendix 8).
12. Men must agree to not donate sperm and a woman 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 drug.

4.2. Exclusion Criteria

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

1. Subjects with tumors of mixed small cell and NSCLC histology
2. Central nervous system (CNS) involvement of disease except as follows: Subjects with previously treated CNS metastases that are adequately treated with whole brain radiotherapy (+/- surgery), that are neurologically stable, and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to first dose of MEDI4736 plus ibrutinib. In addition, there must be no clear evidence of radiographically active disease for at least 90 days prior to enrollment.
3. Anti-tumor therapy (chemotherapy, antibody therapy, immunotherapy, biologic-based therapy, molecularly- targeted therapy, radiation therapy or investigational agent) within 21 days of study Day 1 (six weeks for nitrosureas, mitomycin C, or antibody or molecular targeted agents with $t_{1/2}$ >10 days; 10 weeks for radio- or toxin-immunoconjugates); concurrent use of hormone deprivation therapy including but not limited to anastrozole, letrozole, or tamoxifen citrate for breast cancer and hormonal replacement therapy for non-cancer related conditions is permitted. Enrollment of subjects that have received molecularly-targeted small molecule inhibitors less than 21 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.
4. Prior treatment with ibrutinib or other BTK inhibitor, anti-CD137 or anti-cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) antibody. The following are exceptions to this criterion:
   - Subjects previously treated with anti-PD1, anti-PD-L1, or anti-PD-L2 antibody
5. Known allergy or hypersensitivity to ibrutinib or MEDI4736 or any excipients
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. 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 1 diabetes mellitus; multiple sclerosis; systemic lupus erythematosus; Wegener's granulomatosis; myasthenia gravis; Graves' disease; rheumatoid arthritis; hypophysitis; uveitis; etc) 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's thyroiditis) stable on hormone replacement therapy or psoriasis not requiring systemic treatment
8. History of allogeneic organ transplant
9. 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
10. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to CTCAE (v 4.03), Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of stable neuropathy, vitiligo and alopecia or other irreversible toxicity not reasonably expected to be exacerbated by study treatment (eg, hearing loss)
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. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug (Note: Subjects, if enrolled, should not receive live vaccines during the study and until 180 days after the last dose of study drugs)
14. Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug
15. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV).

    Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
16. History of primary immunodeficiency

17. Known history of previous clinical diagnosis of tuberculosis
18. Any uncontrolled active systemic infection or pneumonitis or interstitial lung disease
19. Major surgery within 4 weeks of the first dose of study drug
20. 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.
21. 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; or a history of myocardial infarction, uncontrolled hypertension or cardiac arrhythmia, unstable angina, or acute coronary syndrome within 6 months prior to enrollment (Appendix 6)
22. Unable to swallow capsules or active malabsorption syndrome not controlled by medication, disease or conditions significantly affecting gastrointestinal function, or complete resection of the stomach, or complete resection of small bowel, or partial or complete bowel obstruction
23. Concomitant use of warfarin or other Vitamin K antagonists
24. Treatment with a strong CYP3A inhibitor (Appendix 5)
25. Pregnant or lactating female; men planning to father a child or women planning a pregnancy while taking study drug or within 3 months after the last dose of study drug
26. Concurrent enrollment in another clinical study, unless in a follow-up period or it is an observational study.
27. Unwilling or unable to participate in all required study evaluations and procedures
28. 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)

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 met all requirements of the inclusion/exclusion criteria, study site personnel can enroll the subject. All enrolled subjects will receive open-label ibrutinib capsules and MEDI4736.

Two dose levels of ibrutinib (560 or 420 mg/day) and MEDI4736 (10 or 3 mg/kg IV Q2 weeks) may be tested (Table 1). The starting dose will be 560 mg of ibrutinib PO daily and 10 mg/kg of MEDI4736 IV Q2 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 acute toxicities.

Phase 1b:

Subjects will be enrolled in up to 4 dose cohorts (1, -[minus]1A, -1B, or -2) regardless of tumor type (for dose levels see Table 1). Assignment of subjects to the two parallel dose de-escalation cohorts (-1A and -1B) will be concurrent and in the sequence of -1A followed by -1B. However, when one dose de-escalation cohort needs additional 3 subjects to evaluate DLTs, all available subjects will be assigned to this cohort first. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter.

Phase 2:

Subjects will be treated at the RP2D as determined in Phase 1b. There will be no stratification of subjects within the pancreatic tumor type cohort. However, in the NSCLC cohort, subjects with adenocarcinoma or squamous-cell carcinoma will be enrolled at an approximate 2:1 ratio (ie, at least 15 subjects with squamous-cell carcinoma will be enrolled). In the breast cancer cohort, subjects with triple-negative or HER2-positive breast cancer will be enrolled at an approximate 2:1 ratio (ie, 15 subjects with triple-negative breast cancer will be enrolled).

5.2. Phase 1b Dose De-escalation and Stopping Rules

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 first 28 days of therapy. The DLT observation period includes Cycle 1 and laboratory assessments 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 first 28 days (Cycle 1=28 days and including laboratory assessments on Day 1 Cycle 2) of 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 1) will be enrolled.

Cohorts -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 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, potentially taking pharmacokinetics and pharmacodynamics aspects into consideration. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter.

Enrollment in a cohort 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, then 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 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 to receive the same dose of study drugs even if a dose de-escalation occurs for other study subjects.

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

5.3. Definition of Dose-Limiting Toxicity (DLT)

The assessment of DLT will follow the guidelines provided in the CTCAE v 4.03. A DLT is defined as any Grade 3 or higher non-hematologic or Grade 4 hematologic AE possibly related to study drug(s) occurring during the DLT observation period with the following clarifications for the toxicities below:

- Grade 4 vomiting or Grade 3 nausea and vomiting despite maximum medical supportive care and persisting >3 days
- Grade 3 or 4 diarrhea despite maximum medical supportive care and persisting >7 days
- Grade 3 fatigue persisting >7 days
- Grade 3 neutropenia lasting >7 days or with fever
- Grade 3 infusion reaction that does NOT resolve with appropriate clinical management

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

- Missed >4 consecutive doses or missed 7 total doses of ibrutinib.
- Missed dose of MEDI4736 or received the MEDI4736 dose outside of the protocol-allowed window (±2 days).

- Study drug discontinuation for any reason other than DLT (ie, including PD).

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

5.4. Study Treatment

All eligible subjects will be treated with ibrutinib PO and MEDI4736 IV in 28-day cycles. On infusion days where pharmacokinetic, pharmacodynamic or biomarker samples are taken post dose, MEDI4736 IV should be given first, followed by that day's ibrutinib dose. Missed doses of ibrutinib and MEDI4736 will not be made up. Dose escalation of any agent (ibrutinib or MEDI4736) at any time will not be allowed. MEDI4736 will be given for a maximum of 12 months. Re-treatment with MEDI4736 will not be allowed following completion of 12 months of treatment, regardless of any dose delays or missed doses. Treatment with ibrutinib will continue for up to 3 years or until disease progression or unacceptable toxicity.

5.4.1. 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 2 week) may be tested. The starting dose will be 560 mg ibrutinib PO daily and MEDI4736 10 mg/kg IV every 2 weeks.

5.4.2. Phase 2

Subjects will be administered ibrutinib and MEDI4736 at the RP2D determined during the Phase 1b portion of the study.

5.5. Study Medication

5.5.1. Ibrutinib

5.5.1.1. 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 IB 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.

5.5.1.2. 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 5).

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 the end of the MEDI4736 infusion), after which subsequent dosing is typically on an outpatient basis. Subjects will be provided a daily drug diary to record ibrutinib doses. Ibrutinib will be dispensed to subjects in bottles at appropriate visits. When a new bottle 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.

5.5.1.3. Overdose

Any dose of study drug administered 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 experience in the management of ibrutinib overdose in patients. No MTD was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11 for further information regarding AE reporting.

5.5.1.4. Dose Modification for Adverse Reactions

The dose of ibrutinib should be modified according to the dose modification guidance in Table 2 if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/µL) for more than 7 days. See Sections 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).*

In the event that the investigator feels deviation from the recommendations above is required, please consult the medical monitor to discuss for approval.

If the dose of ibrutinib is reduced, at the Investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Dose changes must be recorded in the Dose Administration eCRF.

Table 2. 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

If TLS is diagnosed, follow the institutional guidelines for management.

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

For required dose modification for hepatic impairment refer to Section 5.5.1.5 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.

5.5.1.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh class B or C) are excluded from study

participation. For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib to a level of 280 mg daily (two capsules). For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 9).

5.5.2. Durvalumab (MEDI4736)

5.5.2.1. 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.

5.5.2.2. 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 Day 1 and then every 2 weeks thereafter for up to 12 months, regardless of any dose delays or missed doses.

MEDI4736 will be administered as an IV infusion approximately 1 hour in duration (including the IV line flush). The MEDI4736 dose will be calculated using the subject's weight at baseline. This dose should be used for each MEDI4736 administration, unless there is a >10% weight change. In the case of a >10% weight change, the weight at the MEDI4736 dose administration visit should be used to calculate the dose.

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 will 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. The ibrutinib dose should be given within 15 minutes after the end of the MEDI4736 infusion.

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessments. 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. Acetaminophen and/or an antihistamine (eg, diphenhydramine), steroids, or equivalent medications 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.

5.5.2.3. 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.

5.5.2.4. Dose Modification for Adverse Reactions

Refer to Section 6.1 for use of corticosteroids as concomitant medications.

The table below outlines the MEDI4736 Toxicity Management Guidelines.

<table>
<tr><th colspan="4">Immune-Mediated Reactions</th></tr>
<tr><th></th><th colspan="2">Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td rowspan="4">Immune-related Adverse Events (Overall Management for toxicities not noted below)</td><td colspan="2">Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.</td><td rowspan="4">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
• For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent
• If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥28 days of taper)
• More potent immunosuppressives – TNF inhibitors (eg, infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids
• 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.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that subject.</td></tr>
<tr><td>Grade 1</td><td>No dose modification</td></tr>
<tr><td>Grade 2</td><td>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
• Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper
• Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the subject is clinically</td></tr>
</table>

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		stable as per Investigator or treating physician's clinical judgment, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	
	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue study drug/study regimen Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	
Pneumonitis/ Interstitial lung disease (ILD)	Grade of Pneumonitis (CTCAE v 4.03)	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 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 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	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 (Symptomatic, medical intervention indicated, limiting instrumental	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4	For Grade 2 (Mild to Moderate New Symptoms): • Monitor symptoms daily and consider hospitalization • Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day or IV equivalent) • Reimaging as clinically indicated • If no improvement within 3-5 days, additional

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	ADL)	• If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment. • Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to Grade ≤1 and 5-7 days have passed after completion of steroid taper	workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 3-5 days IV methylprednisone at 2-4 g/kg/day, promptly start, immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii] [2] • Consider pulmonary and infectious disease consult • Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening): • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Obtain pulmonary and infectious disease consult • Hospitalize the subject • Supportive Care (oxygen, etc.) • If no improvement within 3-5 days, additional workup and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii]
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE v 4.03)	Any Grade	• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) • Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections, including testing for clostridium difficile toxin

[2] ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			etc.) • Steroids should be considered in the absence of clear alternative etiology, 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 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea: • Close monitoring for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	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 • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to Grade ≤1 and 5-7 days have passed after completion of steroid taper.	For Grade 2 diarrhea: • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide • Promptly start prednisone 1 to 2 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 despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5 mg/kg once every 2 weeks[2 3]) Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Consult study physician if no resolution to ≤Grade 1 in 3-4 days • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[3] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	For Grade 3 or 4 diarrhea: • -Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging and/or colonoscopy as appropriate • If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5mg/kg once every 2 weeks) • Caution: Ensure GI consult to rule out perforation and refer to infliximab label for general guidance before using infliximab. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs) Infliximab should not be used for management of Immune Related Hepatitis	Grade of Liver Function Test Elevation (CTCAE v 4.03) 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 (AST or ALT >ULN to 3 times ULN and/or TB >ULN to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	For Grade 1 AST or ALT and/or TB elevation • Continue LFT monitoring per protocol
	Grade 2 (AST or ALT >3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	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 improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once	For Grade 2 AST or ALT and or TB elevation: • Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. • If no resolution to ≤Grade 1 in 1-2 days, discuss with study physician. • If event is persistent (>3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent • If still no improvement within 3-5 days, despite 1-2 mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone,

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		event stabilizes to Grade ≤1 and 5-7 days have passed after completion of steroid taper	promptly start immunosuppressives (eg, mycophenolate mofetil)[4]. Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, , antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB >3.0-10 times ULN	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 drug/study regimen • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria(ALT>3x ULN + bilirubin >2x ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the	For Grade 3 or 4 AST or ALT and/or TB elevation: • Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent • If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. • Hepatology consult, abdominal workup, and imaging as appropriate • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[4] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" , by Michael Postow MD

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		absence of any alternative cause[iv]	
	Grade 4	Permanently discontinue study drug/study regimen	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine	Grade of Elevated Serum Creatinine (CTCAE v 4.03) Any Grade		• Consult with Nephrologist • Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) • Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections etc.) • Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine >1-1.5X baseline; >ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: • Monitor serum creatinine weekly and any accompanying symptom o If creatinine returns to baseline, resume its regular monitoring per study protocol. o If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine >1.5-3.0 X baseline; >1.5X-3.0XULN]	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 Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 for 5-7 days have passed after completion of steroid taper	For Grade 2 elevated creatinine: • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult Nephrologist and consider renal biopsy if clinically indicated • If event is persistent (>3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			• When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: Serum Creatinine >3.0 X baseline; >3.0-6.0 X ULN	Permanently discontinue study drug/study regimen	• Carefully monitor serum creatinine on daily basis • Consult Nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started.
	Grade 4: Serum Creatinine >6.0 X ULN)		• Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	Any Grade	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED** **
	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 • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after	For Grade 2 : • Obtain dermatology consult • 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 despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and consider systemic steroids prednisone 0.5 to 1 mg/kg/day or IV equivalent • Consider skin biopsy if persistent for >1-2 weeks or recurs

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		completion of steroid taper	
	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: • Consult dermatology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Consider hospitalization • Monitor extent of rash [Rule of Nines] • Consider skin biopsy (preferably more than 1) as clinically feasible. • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade Depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)		• Consult endocrinologist • 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 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 (Depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC 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 indicated and consider endocrinology consult
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI	Hold study drug/study regimen dose until resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3	For Grade 2: (including those with symptomatic endocrinopathy) • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	CTCAE v4.03 for defining the CTC Grade/severity 2)	or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper • Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	• 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, corticosteroids (eg, 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones) • Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE v 4.03 for defining the CTC grade/severity 3 or 4)	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled • Resume study drug/study regimen administration if controlled at the next scheduled dose Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to	For Grade 3 or 4: • Consult endocrinologist • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • Administer hormone replacement therapy as necessary • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate IV corticosteroids with mineralocorticoid activity • Once improving, gradually taper immunosuppressive steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer- related infections [Category 2B recommendation])

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		grade ≤1 and 5-7 days have passed after completion of steroid taper	• Discuss with study physician
Immune-mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillian-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity, refer to NCI CTCAE v 4.03 for defining the CTC grade /severity		
	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	See "Any Grade" recommendations above.
	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. o If toxicity worsens then treat as Grade 3 or Grade 4 o If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to	• Discuss with study physician • Consider Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) • Promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent • If no improvement within 3-5 days, despite 1-2 mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IVIG)

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		Grade ≤1 and 5-7 days have passed after completion of steroid taper	
	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 • Obtain neurology consult • Consider hospitalization • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • If no improvement within 3-5 days, consider additional workup and treatment with additional immunosuppressants (eg, IVIG) • Once stable, gradually taper steroids over ≥4 weeks
	Grade 4	• Permanently discontinue study drug/study regimen	
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 started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 1	No dose modification	• Discuss with the study physician • Care should be taken to monitor subjects for

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			sentinel symptoms of a potential decompensation as described above • Obtain 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 signs of autonomic instability	Grade 2 : • Discuss with the study physician • Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above • Obtain Neurology Consult • 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 IVIG. 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 started with IVIG and followed by plasmapharesis if not responsive to IVIG.

<table>
<tr><th colspan="4">Immune-Mediated Reactions</th></tr>
<tr><th></th><th colspan="2">Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td rowspan="2"></td><td>Grade 3</td><td>• 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</td><td rowspan="2">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 plasmapharesis or IVIG.
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 started with IVIG and followed by plasmapheresis if not responsive to IVIG.</td></tr>
<tr><td>Grade 4</td><td>Permanently discontinue study drug/study regimen</td></tr>
</table>

Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
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 Subsequent infusions may be given at 50%	

Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
	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)

Non-immune Mediated Reactions **(Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"**		
CTC Grade/Severity	**Dose Modification**	**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 regimen until resolution to Grade ≤1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline For AEs that downgrade to Grade ≤2 within 7 days or resolve to Grade ≤1 or baseline within 14 days, resume study drug/study regimen administration 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

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.

[i] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

[ii] NCI CTCAE v4.03

[iii] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

[iv] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

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

5.6. 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 complete 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 Section 5.3 and 9.2 will not be replaced. A Treatment Termination Visit (Section 8.2.3) and End-of-Treatment Visit (Section 8.3.1) are required for all subjects except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be collected from the time of ICF signing or 14 days prior to the first dose, whichever is greater, 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 ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Hormonal or bone sparing treatment are permitted with approval of the Medical Monitor.

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 and infusion reactions) 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. Doses higher than this are permitted only for infusion prophylaxis/reactions or for acute toxicity management.

If corticosteroid treatment for study drug related adverse events with >10 mg per day of prednisone or equivalent is needed, MEDI4736 should be held until the event resolves to Grade ≤1 or baseline and the Medical Monitor should be contacted. Thereafter, MEDI4736

administration may be resumed at the next scheduled dose (also see Section 5.5.2.4 for Dose Modifications for Adverse Reactions).

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 CYP3A4 or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of the inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Appendix 5).
- No dose adjustment is required in combination with mild inhibitors.

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction (see Section 5.5.1.2).

A list of common CYP3A inhibitors and inducers is provided in Appendix 5; For further information, please refer to the current version of the IB and examples of inhibitors, inducers, and substrates can 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. 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 gastrointestinal 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, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Prohibited Concomitant Medications

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

Transfusional support is prohibited for at least 7 days prior to Screening. Pegylated G-CSF (pegfilgrastim) and darbepoetin 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 management, eg pneumonitis or other immune-related AEs, or non-cancer related medical reasons per guidance in Section 6.1

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, lumbar puncture [other than shunt reservoir access], 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 as soon as possible and until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

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 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).

7.1.1.3. Medical History, Risk Factors 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. Details of any cancer risks will be identified (to include family history of cancer, history of being >30 lbs overweight, radiation therapy before the age of 30 [specify location], alcohol ingestion, smoking/tobacco use, chronic pancreatitis, known genetic abnormality [eg, KRAS etc]). 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 the time of ICF signing or from 14 days before the start of study drug, whichever is greater, through 30 days after the last dose of ibrutinib and 90 days after the last dose of MEDI4736. 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 SAE definition must be recorded from the time the ICF is signed until 30 days after the last dose of ibrutinib and 90 days after the last dose of MEDI4736. AEs will be recorded in the electronic case report forms (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 90 days after the last dose of MEDI4736. Laboratory abnormalities designated clinically significant by the Investigator will also be recorded as AEs. Additional important requirements for AE and SAE reporting are explained in Section 11.4.

7.1.1.6. Routine Physical Examination

The Screening, Day 1 of each Cycle, Treatment Termination Visit and End-of-Treatment Visit for ibrutinib or the 90-Day Follow-Up Visit for MEDI4736, 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 4.

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.

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

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will be performed at the site's local laboratory and will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, uric acid, magnesium and bicarbonate. Amylase and lipase should be obtained at Screening, and any time during the study if clinically indicated for evaluation of pancreatitis.

7.1.2.3. Thyroid Stimulating Hormone (TSH)

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 PT/INR, and PTT/aPTT will be performed at the site's local laboratory.

7.1.2.5. Tumor Markers

Tumor markers specific to each tumor type, as noted below, will be performed using the site's local laboratory.

- Pancreatic Cancer - CA 19-9
- Breast Cancer - CA 15-3 and CA 27.29
- NSCLC - CA-125 and carcinoembryonic antigen (CEA)

7.1.2.6. Creatinine Clearance

Creatinine clearance will be measured at the site's local laboratory and calculated using the Cockcroft-Gault method or determined by 24-hour creatinine clearance collection.

7.1.2.7. Hepatitis Serologies

Hepatitis serologies will be performed the site's local laboratory and will include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody will be evaluated. Subjects with chronic or active hepatitis B or C as diagnosed by serologic tests are excluded from the study. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B or C DNA must be performed and must be negative for enrollment.

7.1.2.8. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose and will be performed at the site's local laboratory. Urinalysis will be performed as outlined in Section 8.

7.1.2.9. 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 serum or urine pregnancy test will also be performed on Day 1 prior to the first dose of study drug. If positive, pregnancy must be ruled out by ultrasound to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.1.3. Diagnostics/Procedures

7.1.3.1. ECG

12-lead ECGs should be performed in triplicate with a 1-minute time lag (within 5 min) between each measurement at Screening and for all 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. Tumor Measurements

7.1.3.2.1. CT/MRI

Documented tumor measurement is required using CT scans, positron emission tomography / computed tomography (PET/CT) or MRI, as appropriate, and are to be performed after 2 cycles of treatment and then after every 3 cycles of treatment. The same method of assessment (CT, PET/CT or MRI) and the same technique for acquisition of data must be used to characterize each identified and reported lesion at baseline and at follow-up.

Pretreatment tumor assessment will be performed within 28 days before the first dose of study drug. A CT scan (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites is required for the pretreatment tumor assessment. An adequate volume of contrast should be given to ensure metastases are well-visualized and the method of administration (dose and rate) should be consistent for subsequent examinations. Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the neck and chest without contrast.

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. The PET must be performed prior to the CT with IV contrast as to not compromise PET results. Additionally, 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 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.

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 (eg, central imaging vendor). At the Sponsor's discretion, the Sponsor or its designee may conduct an independent review of the investigator responses.

7.1.3.2.2. Tumor Assessment by Physical Examination

Documented tumor measurement by physical examination (ie, superficial soft tissue lesions, skin lesions, etc.) is required for tumor lesions meeting RECIST 1.1 criteria but only if not assessable using CT scans, positron emission tomography / computed tomography (PET/CT) or MRI, as appropriate, and is to be performed after 2 cycles of treatment and then after every 3 cycles of treatment. The same method of assessment (physical examination) must be used to characterize each identified and reported lesion at baseline and at follow-up.

Pretreatment tumor assessment by physical examination, as appropriate will be performed within 28 days before the first dose of study drug.

7.1.3.3. Tumor Tissue Biopsy

Mandatory tumor biopsy (fresh or archived FFPE if within the last 3 months and after the last systemic anticancer treatment) unless the tumor is inaccessible or the procedure places the subject at a safety risk (ie, locally advanced pancreatic cancer), will be obtained before study

treatment in Phase 2; in Phase 1b, these are optional. Another optional biopsy will be collected at disease progression. 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 for analysis; other biomarkers that predict sensitivity or resistance to the drug combination may also be explored.

7.1.3.4. 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.

7.1.3.5. 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. Refer to the Schedule of Assessments (Appendix 1 and Appendix 2) and the Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, Biomarkers in Appendix 3, and Lab Collection Flowsheet.

7.1.3.6. Biomarkers and Pharmacodynamics Studies

Samples collected may be used for pharmacodynamics and biomarker assessments including ITK and other kinase activity and signaling, soluble PD-L1, ADA immunogenicity, drug occupancy, expression analysis, genomic sequencing, flow cytometry and secreted protein analyses. Fluids including blood, ascites, or pleural fluid collected during the course of the study may be used for, but not limited to, pharmacodynamics 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.

For molecular profiling of tumor samples, DNA/RNA may be extracted for expression and genomic profiling.

Refer to the Schedule of Assessments (Appendix 1 and Appendix 2) and the Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, Biomarkers in Appendix 3, and Lab Collection Flowsheet.

7.1.3.6.1. T/B/NK Counts

The blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be collected before dosing at the protocol-specified time points. Percentages and absolute counts of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16/56^+$ cells will be determined.

7.1.3.6.2. Flow Cytometry-based Whole Blood Assays

Immunophenotyping of subject's blood before and after ibrutinib and MEDI4736 treatment will be performed by staining for T, B, and NK cells, monocytes and other markers.

7.1.3.6.3. Molecular Markers

Cytokines, chemokines, cell surface markers and genomic markers will be tested in peripheral blood, tumor tissue and buccal swabs. If skin biopsies or other specimen are available, they may also be evaluated. Samples will be collected from all subjects.

Samples may also be tested to evaluate other potential biomarkers related to disease and treatment response and to investigate potential mechanisms of treatment resistance. These samples may be characterized by technologies such as gene expression profiling, targeted sequencing for genomic alterations, and intracellular pathway analyses. Inhibition of BTK, ITK and non-BTK and other related kinases may also be explored. These efforts may identify biomarkers that could assist with future development of this compound. Pharmacodynamics assays, ie, BTK and ITK occupancy, may be performed to correlate results of biomarker assessments to the physiological effects of ibrutinib.

7.2. Efficacy Evaluations

All subjects in the study will have their response assessed using the RECIST 1.1 guidelines (Eisenhauer 2009). In the event of symptomatic deterioration due to underlying disease, as determined by the investigator, the investigator should define the criteria for discontinuation of study drug (eg, if related to disease progression or other causes). Grading for best response will be categorized as CR, PR, SD, or PD. Additional information can be found in https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf

Confirmatory scans will be obtained ≥4 weeks after the initial documentation of an objective response.

7.2.1. Definitions

Response and progression will be evaluated in this study using RECIST 1.1 guidelines (Eisenhauer 2009). In the event of symptomatic deterioration due to underlying disease, as determined by the investigator, the investigator should define the criteria for discontinuation of study drug (eg, if related to disease progression or other causes). Changes in the longest diameter

(unidimensional measurement) of the tumor lesions and the short axis for lymph nodes are used in the RECIST 1.1 guidelines.

NOTE: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

7.2.1.1. Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for tumor lesions or short axis for lymph nodes to be recorded) with a minimum size as follows:

- 10 mm with CT scan with a slice thickness of no greater than 5 mm. 10 mm caliper measurement by clinical exam.
- If the slice thickness is >5 mm, the minimum size for a measurable lesion is twice the slice thickness.

Lymph nodes can only be considered as target lesions if they are ≥15 mm in the short axis. Although lymph nodes ≥10 mm is considered pathological, they cannot be categorized as target lesions in RECIST 1.1 guidelines.

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

Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

7.2.1.2. Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using spiral CT or MRI scan, or by physical examination if the lesion is not assessable by CT scan, or pathological nodes with ≥10 to <15 mm short access) as well as truly non-measurable lesions are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable disease.

7.2.1.3. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at the baseline/screening assessment. Target lesions should be selected on the basis of their size (tumor lesions with the longest diameter and lymph nodes with the short axis) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response. Lesions that have been irradiated cannot be included in the tumor assessment, unless unequivocal tumor progression has been documented in these lesions after radiation therapy.

7.2.1.4. Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at the baseline/screening assessment. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence (or in rare cases unequivocal progression) of each should be noted throughout follow-up. Measurements are not required and these lesions should be followed as ‘Complete Response (CR)’, ‘Incomplete Response/Stable Disease (SD)’, or 'Progressive Disease (PD)’. Recording several lesions involving the same organ as a single item is acceptable.

7.2.1.5. New Lesions

If new lesions appear and there is doubt as to whether a lesion is new or an inflammatory change, follow-up scans are required. If the new lesion is confirmed, as unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to be something other than the tumor by a scan obtained at least 4 weeks after the initial scan), the date of progression is taken to be the date on which the new lesion was first detected. If a lesion reappears after disappearing in a subject with CR, PD is declared. However, if such a lesion behaves in this manner in a subject with SD or PR, it is the change in sum of diameters that defines the response or progression.

A lesion found in a follow-up study in a region that was not scanned at baseline is still considered a new lesion and will indicate PD, if confirmed by a repeat scan obtained at least 4 weeks after the initial scan.

7.2.2. Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

Measurements need not be along the same axis (as measured at baseline), but should always be the longest axis of the lesion at that point in time. It does not have to be at the same slice

position, provided the measurement is of the same lesion. However, if the initial measurements are in the axial plane, all further measurements of that lesion must remain in the axial plane. Likewise, if the initial measurements are in the coronal plane (this is acceptable), all further measurements of that lesion must be in the coronal plane.

If a lesion disappears, the measurement of that lesion is clearly 0 mm; however, if the lesion remains present, but is too small to measure accurately, a default measurement of 5 mm should be given, regardless of slice thickness. If lymph nodes decrease to <10 mm, these are considered to be disease free, but remain target lesions. If lesions merge, the long axis of the resulting lesion is measured as one lesion in place of the individual lesions. If lesions split, the long axis of each individual lesion is added together.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Nodal lesions: If lymph nodes are chosen as target lesions and decrease to normal size (<10 mm), the measurement of the lesion must still be included in the sum of the target lesions. This means that subjects may still meet the criteria for CR even if the sum of target lesions is not zero.

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

Tumor markers: Tumor markers alone cannot be used to assess response.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases (eg, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

NOTE: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and PD.

7.2.3. Response Criteria

7.2.3.1. Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Tumor flares:

Delayed responses after a tumor flare have been reported in subjects who have received immune-based therapy. Caution must be exercised not to confuse a possible tumor flare with PD. It is recommended that a biopsy is performed (if lesion is assessable) in order to rule out tumor necrosis and/or an inflammatory reaction) or the lesion is reassessed radiographically, and if there is continued evidence of tumor progression, the date of PD will be documented as the previous evaluation (See Section 3.1 for further details).

7.2.3.2. Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions and/or appearance of one or more new lesions.

7.2.3.3. Evaluation of Best Overall Response

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

Table 3. Time Point Response: Subjects with Target (+/– Non-target) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

7.2.3.4. Missing Assessments or Inevaluable Lesions

When an imaging assessment is not done or a lesion is not evaluable at a particular time point, usually the subject is considered not evaluable (NE) at that time point.

7.2.4. Confirmatory Measurement

7.2.4.1. Confirmation

To be assigned a status of PR or CR as the best overall response, changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥4 weeks after the criteria for response are first met.

In the case of SD, measurement must have met the SD criteria at least once after study entry at a minimal duration of 6 weeks from Study Day 1.

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 and 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 if taken after most recent treatment.

8.1.1. Screening/Consenting Visit

The following procedures will be performed during Screening:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate, 1 minute apart (within 5 min)
- Tumor biopsy (Optional for Phase 1b, required for Phase 2)
- Review of prior medications
- Imaging by CT/MRI

- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - TSH
  - Coagulation (PT, PTT/aPTT, INR)
  - Disease-specific tumor markers
  - Creatinine Clearance
  - Serum pregnancy test (for women of childbearing potential only)
  - Hepatitis serologies
  - Urinalysis
- Research laboratory blood samples:
  - Biomarkers and pharmacodynamics

8.2. Treatment Phase

8.2.1. Treatment Visits

8.2.1.1. Cycle 1 Day 1 (C1D1)

Laboratory assessments performed within 48 hours of C1D1 may be used as predose C1D1 laboratory assessments and are not required to be repeated. Predose laboratory test results for eligibility (*) must be reviewed to confirm eligibility prior to start of treatment.

Predose

- Confirmation of eligibility
- Complete physical exam
- ECOG Performance Status
- Vital signs (within 30 min of MEDI4736 infusion start) and weight
- 12-lead ECG (in triplicate, 1 minute apart (within 5 min) 30-60 minutes prior to MEDI4736 infusion start
- Clinical laboratory tests for:
  - Hematology*
  - Serum chemistry*
  - TSH
  - Disease-specific tumor markers
  - Pregnancy test (for women of childbearing potential only)*

- Urinalysis
- Research laboratory blood samples collected pre-dose for:
  - Pharmacokinetics
  - Biomarkers and pharmacodynamics
  - Buccal swab
- Review of concomitant medications

Dosing

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

Postdose

- Vital signs at the following time points:
  - End of MEDI4736 infusion (+5 minutes)
  - 30 minutes (±5 minutes) post end of MEDI4736 infusion
  - 60 minutes (±5 minutes) post end of MEDI4736 infusion
- 12-lead ECG (in triplicate, 1 minute apart (within 5 min) 2 h and 4 h post ibrutinib dose
- Research laboratory blood samples (see Appendix 3 for collection schedule):
  - Pharmacokinetics
  - Biomarkers and pharmacodynamics
- Review of AEs and concomitant medications
- Dispense ibrutinib bottle to subject

8.2.1.2. Cycle 1 Day 2 (C1D2)

Predose

- Research laboratory blood samples:
  - Pharmacokinetics (24 h time point from Day 1)
  - Biomarkers and pharmacodynamics (24 h time point from Day 1)

Dosing

- In-clinic administration of ibrutinib

8.2.1.3. Cycle 1 Day 8 (C1D8) (for Phase 1b only)

- Brief physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications

8.2.1.4. Cycle 1 Day 15 (C1D15)

Predose

- Brief physical exam
- ECOG Performance Status
- Vital signs (within 30 mins of MEDI4736 infusion start) and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Research laboratory blood samples:
  - Pharmacokinetics
  - Biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

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

Postdose

- Vital signs at the following time points:
  - End of MEDI4736 infusion (+5 minutes)
  - 30 minutes (±5 minutes) post end of MEDI4736 infusion
  - 60 minutes (±5 minutes) post end of MEDI4736 infusion

- Research laboratory blood samples (see Appendix 3 for collection schedule):
  - Pharmacodynamics
- Review of AEs and concomitant medications

8.2.1.5. Cycle 1 Day 22 (C1D22) (for Phase 1b only)

- Brief physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
- Review of AEs and concomitant medications

8.2.1.6. Day 1 of Each Subsequent Cycle

Subjects must continue to come in on Day 1 of each cycle for the first 15 cycles. After this time, subjects must come in on Day 1 of every 3rd cycle.

Predose

- Complete physical exam
- ECOG Performance Status
- Vital signs (within 30 mins of MEDI4736 infusion start) and weight
- Cycle 3 and 5 only – 12-lead ECG (in triplicate, 1 minute apart [within 5 min]) 30–60 minutes prior to MEDI4736 infusion start
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - TSH (Day 1 each cycle while being treated with MEDI4736 until Cycle 13 and at the 90-day follow-up visit)
  - Disease-specific tumor markers
  - Urinalysis (Beginning at Cycle 1 and then every 3 cycles, [eg, Cycle 4 Day 1, Cycle 7 Day 1, Cycle 10 Day 1, etc] during the MEDI4736 infusion period and at the 90-day Follow-Up Visit)
  - Pregnancy test (if applicable)
- Research laboratory blood samples (see Appendix 3 for collection schedule):
  - Pharmacokinetics

- Biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

- In-clinic administration of MEDI4736
- Vital signs every 15 minutes (±5 minutes) during MEDI4736 infusion
- Review subject dosing diary and dispense ibrutinib
- In-clinic administration of ibrutinib (within 15 minutes AFTER the end of MEDI4736 infusion)

Postdose

- Vital signs at the following time points:
  - End of MEDI4736 infusion (+5 minutes)
  - 30 minutes (±5 minutes) post end of MEDI4736 infusion
  - 60 minutes (±5 minutes) post end of MEDI4736 infusion
- Cycle 3 only – 12-lead ECG (in triplicate, 1 minute apart [within 5 min] 2 h and 4 h post ibrutinib dose
- Cycle 5 only – 12-lead ECG (in triplicate, 1 minute apart, [within 5 min] 2 h post ibrutinib dose
- Research laboratory blood samples (see Appendix 3 for collection schedule):
  - Pharmacokinetics
  - Biomarkers and pharmacodynamics
- Review of AEs and concomitant medications
- Dispense ibrutinib bottle to subject

8.2.1.7. Day 15 of Each Subsequent Cycle

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

Predose

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

- Research laboratory blood samples (see Appendix 3 for collection schedule):
  - Biomarkers and pharmacodynamics
- Review of AEs and concomitant medications

Dosing

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

Postdose

- 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
- Review of AEs and concomitant medications

8.2.2. Response Evaluations

Response Evaluation visits will be performed per the schedule outlined in Appendix 1 and Appendix 2. The following procedures will be performed in conjunction with standard visits as follows:

- Radiologic exam by CT and/or MRI at the end of Cycle 2 (Cycle 2 Day 28 [– 7 days]) and then after every 3rd cycle (Cycle x Day 28 [-7 days])
- RECIST 1.1 Response Evaluation
- Research laboratory blood samples (when subject achieved CR and/or at PD, unless taken within the last 7 days):
  - Biomarkers and pharmacodynamics

8.2.3. Treatment Termination Visit (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, or physical examination (if the lesion is not assessable) by any of these modalities may be done per investigator discretion to assess for progressive disease.

The following procedures will be performed:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Pregnancy test
  - Disease-specific tumor markers
- Research laboratory blood samples collected:
  - Biomarkers and pharmacodynamics
- Optional tumor tissue biopsy (if discontinued treatment due to disease progression)
- Review of AEs and concomitant medications

8.3. Follow-up Phase

Once a subject has completed the Treatment Termination Visit, they will enter the Follow-Up Phase. Subjects that withdraw from treatment for reasons other than progressive disease will participate in ongoing response follow-up.

8.3.1. End-of-Treatment Visit for Ibrutinib

An End-of-Treatment Visit should occur 30 days (±7 days) from the last dose of ibrutinib 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 MEDI4736 alone.* An optional tumor tissue biopsy may be collected if treatment was discontinued due to PD.

Subjects who withdraw consent to treatment may still have an 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
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Disease-specific tumor markers
  - Pregnancy test

- Research laboratory blood samples collected:
  - Biomarkers and pharmacodynamics (unless taken within the last 7 days)
- Review of AEs and concomitant medications

8.3.2. 90-day Follow-Up Visit for MEDI4736

A 90-day Follow-Up Visit should occur approximately 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 have a 90-day Follow-Up Visit. The following procedures will be performed:

- Complete physical exam
- ECOG Performance Status
- Vital signs and weight
- Clinical laboratory tests for:
  - Hematology
  - Serum chemistry
  - Urinalysis
  - Disease-specific tumor markers
  - TSH
- Research laboratory blood samples collected:
  - Pharmacokinetics and pharmacodynamics
- Review of AEs and concomitant medications

8.3.3. Response Follow-up

Subjects who discontinue the study for reasons other than PD will be followed every 12 weeks (±7 days) from the last CT or MRI scan until PD, up to 3 years after the first dose of the last subject enrolled. An optional tumor tissue biopsy may be collected at PD. During this period, it is preferred that disease-specific tumor markers and CT or MRI scans are obtained using RECIST 1.1 guidelines.

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 follow up on survival and use of alternative anticancer therapy (including the response and disease progression for the therapy), up to 3 years after the

first 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.

Subjects may receive treatment for up to 3 years, unless they enroll in an extension study, reach the time of the study closure, or discontinue from the study for any reason, whichever occurs first.

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 intercurrent illness or adverse event that prevents further administration of ibrutinib and/or MEDI4736
- Symptomatic deterioration
- Dose-Limiting Toxicity
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
- Lost to follow-up
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo a Treatment Termination and 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 PD, a DLT, or an AE 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. Enrolled Population

This population includes all subjects who were enrolled in Phase 1b and Phase 2.

10.1.2. 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 rate and disease control rate at Week 20 (Cycle 5).

10.1.3. Safety Population

The Safety Population will consist of all enrolled subjects who received at least one dose of study treatment. The Safety Population will be used for the analysis of safety data. This population will also be used for the analyses of progression-free survival and overall survival.

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 will be replaced. For replacement of subjects in the DLT observation period please refer to Section 5.3.

10.2. Endpoints for Phase 1

10.2.1. Primary Endpoints

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

10.2.2. Secondary Endpoints

- Overall response rate (ORR)
- Disease control rate (DCR) at Week 20 (Cycle 5)
- Duration of response (DOR)
- Pharmacokinetics and pharmacodynamics profiles

10.2.3. Exploratory Endpoints

- Immune-cell subsets
- Non-BTK-related pharmacodynamics (ie, EGFR, 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

10.3. Endpoints for Phase 2

10.3.1. Primary Endpoint

- Overall response rate (ORR)

10.3.2. Secondary Endpoints

- Disease control rate (DCR) at Week 20 (Cycle 5)
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Pharmacokinetics and pharmacodynamics profiles

10.3.3. Exploratory Endpoints

- Immune-cell subsets
- Non-BTK-related pharmacodynamics (ie, EGFR, 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

10.4. Sample Size Determination

This study is not powered for comparison of treatment arms.

10.4.1. Phase 1b

Dose de-escalation will follow the 6+3 design described in Section 5.2 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. Up to 4 dose cohorts will be tested. Subjects are considered DLT-evaluable if they receive the assigned dose of study treatment (both ibrutinib 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. If necessary, the dose de-escalation cohort -2 will be enrolled thereafter.

Subjects in Phase 1b who were dosed at the RP2D and with a tumor type as defined for Phase 2 may also be included in the Phase 2 analysis.

10.4.2. Phase 2

Hypothesis for the true response rate will be tested as described below for each cohort independently. With a 1-sided type I error rate of 0.05, each cohort would have 80% power based on true response rate in the alternative hypothesis. Approximately 130 subjects (including 6-9 subjects treated at the RP2D in Phase 1b and with the tumor type as defined for Phase 2) across the three tumor type cohorts will be included in the Phase 2 analyses (an interim analysis and the primary analysis). The Phase 2 statistical design including number of subjects and number of responders for each analysis follows the statistical framework of Simon's optimal two-stage design (Simon, 1989). The enrollment will continue while the interim analysis is performed.

For each cohort, if a subject discontinues prior to the first tumor response assessment for reasons other than progressive disease, the subject may be replaced.

NSCLC cohort and breast cancer cohort (n=18 for the interim analysis and n=43 for the primary analysis for each cohort):

For each of the two tumor type cohorts, a true response rate of 10% (H0) versus 25% (Ha) will be tested and the probability of early stopping is at least 73.4% if the true response rate is ≤10% (H0), and no greater than 13.5% if the true response rate is ≥25% (Ha).

An interim analysis will be performed based on the first 18 evaluable subjects (defined in Section 10.1.2) for each cohort independently. If 2 or fewer responders are observed among the 18 evaluable subjects in a cohort, the enrollment may be stopped. Otherwise, enrollment will continue to enroll an additional 25 evaluable subjects for a total of 43 evaluable subjects for the primary analysis. The null hypothesis will be rejected if 8 or more responders are observed among the 43 evaluable subjects.

For the NSCLC cohort, subjects with adenocarcinoma and squamous-cell carcinoma will be enrolled at an approximate 2:1 ratio (ie, at least 15 subjects with squamous-cell carcinoma will be enrolled).

For the breast cancer cohort, subjects with triple negative or HER2-positive breast cancer will be enrolled at an approximate 2:1 ratio (ie, at least 15 subjects withtriple-negative breast cancer will be enrolled).

Pancreatic cancer cohort (n=17 for the interim analysis and n=44 for the primary analysis):

A true response rate of 5% (H0) versus 18% (Ha) will be tested and the probability of early stopping is at least 79.2% if the true response rate is ≤5% (H0), and no greater than 16.2% if the true response rate is ≥18% (Ha).

An interim analysis will be performed based on the first 17 evaluable subjects. If 1 or no responder is observed among the 17 evaluable subjects, the enrollment may be stopped. Otherwise, the enrollment will continue to enroll additional 27 evaluable subjects for a total of 44 evaluable subjects for the primary analysis. The null hypothesis will be rejected if 5 or more responders are observed among the 44 evaluable subjects.

For NSCLC, 10% was chosen based on the fact that, per NCCN guidelines, the reported second- and third-line response rates to systemic chemotherapy have generally been less than 10% and have limited clinical utility. For HER2-positive breast cancer, response rates and PFS in the relapsed setting are low, especially after multiple lines of prior therapy. For third line, published response rates were 22% and 14% in one study (Geyer 2006). For triple-negative breast cancer, in a Phase 3 study, the response rates were 27% and 9% (Pivot 2009). In combination with these response rates and given the fact that many of these therapies have intolerable side effects, 10% was chosen for breast cancer overall as the futility endpoint. A 25% response rate would be considered clinically meaningful. For pancreatic cancer, in the relapsed setting, the majority of trials had a response rate below 10% (Rahma 2013, Walker 2014), and also based on the fact that treatment options are limited for this population, 5% was chosen as the futility endpoint with ≥18% being worth further study.

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 RECIST 1.1 guidelines for all three tumor types.

10.6.1. Phase 1b Analyses

The primary objective of Phase 1b is to determine the RP2D or MTD 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 AEs

experienced through Phase 1b. Study-drug exposure and laboratory data will be evaluated and summarized by dose cohort and tumor type.

The secondary objectives are to evaluate efficacy and pharmacokinetics / pharmacodynamics in subjects receiving the combination regimen. The ORR along with the corresponding 95% confidence interval based on exact binomial distribution and DOR for responders will be calculated and summarized with descriptive statistics by dose cohort and tumor type. Disease control rate (DCR) at Week 20 (Cycle 5) along with its 95% confidence interval based on exact binomial distribution will be provided by dose cohort and tumor type. Pharmacokinetics and pharmacodynamics data will be summarized by dose cohort and tumor type.

10.6.2. Phase 2 Analyses

Timing of Phase 2 Analysis:

For each tumor type cohort, an interim analysis will be performed to evaluate safety and determine the response rate after the first 18 evaluable subjects for the NSCLC and breast cancer cohorts /17 evaluable subjects for the pancreatic cancer cohort completed at least one tumor response assessment or at least 3 responders in the NSCLC and breast cancer cohorts / 2 responders in the pancreatic cancer cohort were observed, whichever occurs first. Confirmation of response is not required for the interim analysis.

The primary analysis for each cohort will be performed to determine the response rate and safety profile after all subjects included for the Phase 2 analysis have completed at least two tumor response assessments or have progressed prior to the second tumor response assessment. Confirmation of response is required for the primary analysis. A cohort may be discontinued based on the interim efficacy and/or safety results.

The final analysis will be performed at the end of the study (3 years after the first dose of the last subject enrolled) based on all subjects enrolled in this study.

10.6.2.1. Primary Efficacy Analysis

The primary efficacy analysis will be based on ORR using the Response-evaluable Population in each of the three solid tumor cohorts. ORR is the proportion of response-evaluable subjects who achieved a CR or a PR with confirmation. 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

Disease control rate (DCR) at Week 20 (Cycle 5) will be based on the Response-evaluable Population in each of the three solid tumor cohorts. DCR at Week 20 (Cycle 5) is the proportion of response-evaluable subjects who maintain disease control (CR, PR or SD) at Week 20

(Cycle 5). The observed DCR at Week 20 (Cycle 5) along with its 95% confidence interval based on exact binomial distribution will be calculated and summarized for each tumor cohort.

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; censoring conventions for DOR will be provided in the SAP.

Progression-free survival (PFS) and 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 using RECIST 1.1 guidelines 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 conventions for those two endpoints will be described in the statistical analysis plan (SAP).

Pharmacokinetics and pharmacodynamics profiles will be evaluated by tumor type cohort and overall.

10.6.2.3. Exploratory Efficacy Analyses

Subgroup Analyses: For each tumor type cohort, a subgroup analysis will be conducted to calculate response rate and its 95% confidence interval based on PD-L1 expression (positive versus negative). For the NSCLC cohort, a subgroup analysis will also be conducted based on subjects with adenocarcinoma versus squamous-cell carcinoma. For the breast cancer cohort, a subgroup analysis will also be conducted based on subjects with HER2-positive versus triple-negative breast cancer.

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

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

10.7. Safety Analysis

Analysis of safety data will be conducted on the safety population, which includes enrolled subjects who received at least one dose of study drug. 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, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

10.7.1. Adverse Events

Adverse event parameters to be evaluated are the type, incidence, and intensity of adverse events; the relationship of adverse events to study treatment; and the action taken with respect to study treatment due to adverse events.

The verbatim terms used in the eCRF by Investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be defined in the statistical analysis plan.

All treatment-emergent AEs 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 treatment-emergent adverse events will be summarized according to intensity (CTCAE, v4.03) 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 an SAE.

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 International System (SI) unit. Selected hematology and chemistry laboratory parameters are detailed in Section 7.1.2. Laboratory values will be graded using the CTCAE v4.03.

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 (the Medical Monitor or designee, a Drug Safety representative, and a statistician at a minimum).

10.9. Pharmacokinetic Analysis (Ibrutinib, Combination of Ibrutinib and MEDI4736)

Ibrutinib and PCI-45227 bioanalytical data will be used in noncompartmental pharmacokinetics 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 pharmacokinetics summary.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and pharmacokinetics 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-pharmacokinetics analysis using nonlinear mixed effects models. For the population-pharmacokinetics analysis, covariates that could potentially correlate with plasma pharmacokinetics parameters will be evaluated. The results of the population-pharmacokinetics analyses (if performed) will be presented in a separate report.

For the drug combination of ibrutinib and MEDI4736, model-derived exposure parameters (PK parameters) may be used to explore PK/PD correlation between the exposure of ibrutinib and its active metabolites with relevant clinical or biomarker information to assess effectiveness and toxicity.

Ibrutinib and MEDI4736 PK data in this study will be compared to observed/reported concentration data for ibrutinib and MEDI4736 and/or concentration estimates from the existing literature and/or population PK models to explore the potential for a pharmacokinetic interaction between ibrutinib and MEDI4736.

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 pharmacokinetics parameters will be determined after the first or steady-state dose: Peak concentration (C_{max}), 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 pharmacokinetics parameters will be provided.

10.11. Immunogenicity Analyses

Immunogenicity analyses will be performed by determining the anti-MEDI4736 response before and/or after treatment with ibrutinib and MEDI4736 at selected time points during treatment with ibrutinib and MEDI4736.

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 during treatment with ibrutinib and/or MEDI4736. Pharmacodynamic assays for ibrutinib may include occupancy assays of 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 for analysis; other biomarkers that predict sensitivity or resistance to the drug combination may also be explored.

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 adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events 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

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

- Results in death (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 adverse event, it should be recorded on the adverse events eCRF. If the adverse event is considered serious, it should be recorded on the adverse events 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 adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events 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 adverse event or serious adverse event 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 for ibrutinib and/or 90 days after the last dose for 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/or 90 days after 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).

Serious adverse events reported after 30 days following the last dose of ibrutinib and/or 90 days after the last dose of MEDI4736 should also be reported if considered related to any of the study drugs.

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 adverse events, 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 and/or 90 days after the last dose of MEDI4736, the death must be reported to the Sponsor as a serious adverse event.

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

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

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

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 adverse event, 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 must be reported. 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 a serious adverse event.

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 adverse events, or groups of adverse events, 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 of the following:

- 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 v4.03.

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.

In the event of a Grade ≤2 infusion-related reaction, the infusion rate of MEDI4736 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 infusion rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade ≥3 or higher in severity, treatment with MEDI4736 should 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.

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.

For cases in which the aminotransferase and bilirubin elevations meet the Hy's Law criteria threshold, a discussion between the Investigator and the Medical Monitor should take place to determine the evaluation and management of the subject.

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 the 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 of **all** subjects who have consented to enroll 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 MEDI4736 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-1135-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib or MEDI4736 dispensed or 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. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. 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.

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.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, 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.

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14. APPENDICES

Appendix 1. Schedule of Assessments for Phase 1b

Study Visits for Phase 1b	Screening	Treatment-Phase (1 cycle = 28 Days)												Post-treatment				
		Cycle 1					Cycle 2		Cycle 3		Cycle 4 & Beyond		Response Evaluation	Treatment Termination (optional)	End-of-Treatment for ibr	90-day FU for MEDI4736	Response FU (Until PD)	Survival FU (Post-PD)
		D1	D2	D8	D15	D22	D1	D15	D1	D15	D1[g]	D15[h]	End of Cycle 2 & Q3 cycles thereafter	At any time during the study	30 d from last ibr or before next therapy	90 d from last MEDI 4736 dose or before next therapy	Q12 weeks from last CT/MRI scan	Q12 weeks from last dose
Visit Window	*-28 days*	*NA*		*± 2 days*			*-2 days*	*± 3 days*					*-7 days*	*NA*	*± 7 days*		*± 7 days*	*± 7 days*
Procedures																		
Informed consent	X																	
Confirm eligibility (Inclusion/exclusion criteria)	X	X																
Medical history and demographics	X																	
Physical exam	X	X		X	X	X	X	X	X	X	X	X		X	X	X		
ECOG performance status	X	X		X	X	X	X	X	X	X	X	X		X	X	X		
Vital signs[a] and weight (height only at screening)	X	X		X	X	X	X	X	X	X	X	X		X	X	X		
Tumor Biopsy (optional)	X													X At progression (optional)				
12-lead ECG (triplicate)	X	X[b]							X[b]		C5D1[b]							
Prior and concomitant medications	Continuous from ICF or 14 days prior the first dose of study drug (whichever is greater) to 30 days (ibrutinib)/90 days (MEDI4736) after last dose																	
Adverse events		Continuous from ICF to 30 days (ibrutinib)/90 days (MEDI4736) after last dose																
Hematology	X	X		X	X	X	X	X	X	X	X	X		X	X	X		
Serum chemistry	X	X		X	X	X	X	X	X	X	X	X		X	X	X		
TSH	X	X					X		X		X[c]					X		
Coagulation (PT, PTT/aPTT, INR)	X																	
Disease-specific tumor markers	X	X					X		X		X			X	X	X	X	
Creatinine clearance	X																	
Hepatitis serologies	X																	
Pregnancy test (serum at screening, urine at f/u)	X	X					X		X		X			X	X			
Urinalysis	X	X									X[d]					X		
CT/MRI scan	X												X				X	
RECIST 1.1 response evaluation	X												X				X	
Survival status and subsequent antineoplastic therapy,and disease progression																		X

Study Visits for Phase 1b	Screening	Treatment-Phase (1 cycle = 28 Days)												Post-treatment				
		Cycle 1					Cycle 2		Cycle 3		Cycle 4 & Beyond		Response Evaluation	Treatment Termination (optional)	End-of-Treatment for ibr	90-day FU for MEDI4736	Response FU (Until PD)	Survival FU (Post-PD)
		D1	D2	D8	D15	D22	D1	D15	D1	D15	D1[g]	D15[h]	End of Cycle 2 & Q3 cycles thereafter	At any time during the study	30 d from last ibr or before next therapy	90 d from last MEDI 4736 dose or before next therapy	Q12 weeks from last CT/MRI scan	Q12 weeks from last dose
Visit Window	*-28 days*	*NA*		*± 2 days*			*-2 days*	*± 3 days*					*-7 days*	*NA*	*± 7 days*		*± 7 days*	*± 7 days*
PK		Refer to Appendix 3 for sampling schedule																
Biomarkers and Pharmacodynamics	X	Refer to Appendix 3 for sampling schedule																
Buccal swab		X																
Study Drug Administration																		
Dispense ibrutinib & review diary		X					X		X		X							
In-clinic administration of ibrutinib[e]		X	X		X	X	X	X	X	X	X	X						
In-clinic administration of MEDI4736		X			X		X	X	X	X	X[f]	X[f]						

C = cycle, CR = complete response, CT = computed tomography, D or d = day(s), ECG = electrocardiogram, FU = follow-up, ibr = ibrutinib, ICF = informed consent form, INR = international normalized ratio, MRI = magnetic resonance imaging, PD = progressive disease, PK = pharmacokinetics, PT = prothrombin time, PTT = partial thromboplastin time, aPTT = activated partial thromboplastin time, RECIST = response evaluation criteria in solid tumors, TSH = thyroid stimulating hormone

a. Vital signs: On MEDI4736 infusion days, vital signs will be measured within 30 minutes prior to the start of MEDI4736 infusion, every 15 minutes (± 5 minutes) during MEDI4736 infusion, at the end-of- infusion of MEDI4736 (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post end-of-infusion of MEDI4736. On C1D1, C3D1 and C5D1, additional ECGs will be performed (see footnote b).

b. To be performed within 30-60 minutes prior to start of MEDI4736 infusion. In addition, on C1D1 and C3D1, triplicate ECGs will be performed at 2 h and 4 h post ibrutinib dose; on C5D1, triplicate ECGs will be performed at 2 h post ibrutinib dose.

c. At Day 1 each cycle while being treated with MEDI4736 and then 90 Days after the last dose of MEDI4736

d. Beginning at Cycle 4 and then every 3 Cycles during the MEDI4736 infusion period and 90 days after the last dose of MEDI4736.

e. In-clinic administration of ibrutinib should be done within 15 minutes after the end of the MEDI4736 infusion.

f. MEDI4736 dosing should only continue for up to 12 months after the first dose.

g. Subjects must continue to come in on Day 1 of each cycle for the first 15 cycles. After this time, subjects must come in on Day 1 of every 3rd cycle.

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

Appendix 2. Schedule of Assessments for Phase 2

Study Visits for Phase 2	**Screening**	**Treatment-Phase (1 cycle = 28 Days)**										**Post-treatment**				
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 & Beyond		Response Evaluations	Treatment Termination (optional)	End-of-Treatment for ibr	90-day FU for MEDI4736	Response FU (Until PD)	Survival FU (Post-PD)
		D1	D2	D15	D1	D15	D1	D15	D1[g]	D15[h]	End of Cycle 2 & Q3 cycles thereafter	At any time during the study	30 d from last ibr or before next therapy	90 d from last MEDI 4736 dose or before next therapy	Q12 weeks from last CT/MRI scan	Q12 weeks from last dose
Visit Window	*-28 days*	*NA*		*± 2 days*		*± 3 days*					*-7 days*	*NA*	*± 7 days*		*± 7 days*	*± 7 days*
Procedures																
Informed consent	X															
Confirm eligibility (Inclusion/exclusion criteria)	X	X														
Medical history and demographics	X															
Physical exam	X	X		X	X	X	X	X	X	X		X	X	X		
ECOG performance status	X	X		X	X	X	X	X	X	X		X	X	X		
Vital signs[a] and weight (height only at screening)	X	X		X	X	X	X	X	X	X		X	X	X		
Tumor Biopsy	X											X At progression (optional)				
12-lead ECG (triplicate)	X	X[b]					X[b]		C5D1[b]							
Prior and concomitant medications	Continuous from ICF or 14 days prior the first dose of study drug (whichever is greater) to 30 days (ibrutinib)/90 days (MEDI4736) after last dose															
Adverse events		Continuous from ICF to 30 days (ibrutinib)/90 days (MEDI4736) after last dose														
Hematology	X	X		X	X	X	X	X	X	X		X	X	X		
Serum chemistry	X	X		X	X	X	X	X	X	X		X	X	X		
TSH	X	X			X		X		X[c]					X		
Coagulation (PT, PTT/aPTT, INR)	X															
Disease-specific tumor markers	X	X			X		X		X			X	X	X	X	
Creatinine clearance	X															
Hepatitis serologies	X															
Pregnancy test (serum at screening, urine at f/u)	X	X			X		X		X			X	X			
Urinalysis	X	X							X[d]					X		
CT/MRI scan	X										X				X	
RECIST 1.1 response evaluation	X										X				X	
Survival status and subsequent anticancer therapy (including response and disease progression for the																X

Study Visits for Phase 2	**Screening**	**Treatment-Phase (1 cycle = 28 Days)**										**Post-treatment**				
		Cycle 1			Cycle 2		Cycle 3		Cycle 4 & Beyond		Response Evaluations	Treatment Termination (optional)	End-of-Treatment for ibr	90-day FU for MEDI4736	Response FU (Until PD)	Survival FU (Post-PD)
		D1	D2	D15	D1	D15	D1	D15	D1[g]	D15[h]	End of Cycle 2 & Q3 cycles thereafter	At any time during the study	30 d from last ibr or before next therapy	90 d from last MEDI 4736 dose or before next therapy	Q12 weeks from last CT/MRI scan	Q12 weeks from last dose
Visit Window	*-28 days*	*NA*		*± 2 days*		*± 3 days*					*-7 days*	*NA*	*± 7 days*		*± 7 days*	*± 7 days*
therapy)																
PK		Refer to Appendix 3 for sampling schedule														
Biomarkers and Pharmacodynamics	X	Refer to Appendix 3 for sampling schedule														
Buccal swab		X														
Study Drug Administration																
Dispense ibrutinib & review diary		X			X		X		X							
In-clinic administration of ibrutinib[e]		X	X	X	X	X	X	X	X	X						
In-clinic administration of MEDI4736		X		X	X	X	X	X	X[f]	X[f]						

C = cycle, CR = complete response, CT = computed tomography, D or d = day(s), ECG = electrocardiogram, FU = follow-up, ibr = ibrutinib, ICF = informed consent form, INR = international normalized ratio, MRI = magnetic resonance imaging, PD = progressive disease, PK = pharmacokinetics, PT = prothrombin time, PTT = partial thromboplastin time, aPTT = activated partial thromboplastin time , RECIST = response evaluation criteria in solid tumors, TSH = thyroid stimulating hormone

a. Vital signs: On MEDI4736 infusion days, vital signs will be measured within 30 minutes prior to the start of MEDI4736 infusion, every 15 minutes (± 5 minutes) during MEDI4736 infusion, at the end-of- infusion of MEDI4736 (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post end-of- infusion of MEDI4736.

b. To be performed within 30-60 minutes prior to start of MEDI4736 infusion. In addition, on C1D1 and C3D1, triplicate ECGs will be performed at 2 h and 4 h post ibrutinib dose; on C5D1, triplicate ECGs will be performed at 2 h post ibrutinib dose.

c. At Day 1 each cycle while being treated with MEDI4736 and then 90 Days after the last dose of MEDI4736.

d. Beginning at Cycle 4 and then every 3 Cycles during the MEDI4736 infusion period and 90 days after the last dose of MEDI4736.

e. In-clinic administration of ibrutinib should be done within 15 minutes after the end of the MEDI4736 infusion.

f. MEDI4736 dosing should only continue for up to 12 months after the first dose.

g. Subjects must continue to come in on Day 1 of each cycle for the first 15 cycles. After this time, subjects must come in on Day 1 of every 3rd cycle.

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

Appendix 3. Schedule of Assessments for Pharmacokinetics, Pharmacodynamics, and Biomarkers*

Timepoints[a]			Ibrutinib PK	Ibrutinib Biomarker/ Pharmacodynamics [c]	MEDI4736 PK	MEDI4736 Pharmacodynamics
Screening				X		
Cycle 1	Day 1	Predose [b]	X	X	X	X (includes ADA)
		1 hr postdose ibrutinib (± 15 min)	X		X [d]	X [d]
		2 hr postdose ibrutinib (± 15 min)	X			
		4 hr postdose ibrutinib (± 30 min)	X	X		
	Day 2	24 hr postdose Day 1 (± 2 h)	X	X		
	Day 15	Predose [b]		X	X	X
		4 hr postdose ibrutinib (± 30 min)		X		
Cycle 2	Day 1	Predose [b]		X		
	Day 15	Predose [b]		X		
Cycle 3	Day 1	Predose [b]	X	X	X	X (includes ADA)
		1 hr postdose ibrutinib (± 15 min)	X		X [d]	X [d]
		2 hr postdose ibrutinib (± 15 min)	X			
		4 hr postdose ibrutinib (± 30 min)	X			
	Day 15	Predose [b]		X		
Cycle 4	Day 1	Predose [b]		X		
Cycle 5	Day 1	Predose [b]		X		
Cycle 6	Day 1	Predose [b]		X	X	X (includes ADA)
		1 hr postdose ibrutinib (± 15 min)			X [d]	X [d]
Cycles 9, 12, 15	Day 1	Predose [b]		X	X	X (includes ADA)
Cycle 18 & q3 cycles thereafter	Day 1	Predose [b]		X		
At CR and/or Progressive Disease [e]				X		
Treatment Termination Visit (Optional)				X		
End-of-Treatment Visit for ibrutinib (30 Day Follow-up) [e]				X		
90 Day Follow-up Visit for MEDI4736 [e]					X	X

Abbreviations: ADA = anti-drug antibodies; CR = complete response; PK = pharmacokinetics

* Please refer to the PPD Laboratory Flowchart for a complete list of lab samples to be collected at each time point

a. MEDI4736 will be administered as an IV infusion approximately 1 hour in duration. Subjects are expected to take ibrutinib PO within 15 minutes AFTER the end of the MEDI4736 infusion.

b. Predose=predose MEDI4736 infusion and ibrutinib PO

c. This column combines both ibrutinib biomarker and pharmacodynamics (ibrutinib PD CPT) collections. Please refer to the collection flow chart for exact timepoints of each collection.

d. 1-hr post dose ibrutinib is approximately 1 hr (+ up to 15 min) after the end of the MEDI4736 infusion and approximately 2 hr (+ up to 15 min) after the initiation of MEDI4736 infusion. Samples are to be drawn at the same time.

e. If the visit occurs at a routine study visit where the samples are already being drawn, a separate set of samples is not required.

Appendix 4. 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 5. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

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
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

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.

From: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

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. Hepatitis Serology Chart

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

Interpretation of Hepatitis B Serologic Test Results		
HBsAg	negative	Susceptible
anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	Immune due to natural infection
anti-HBc	positive	
anti-HBs	positive	
HBsAg	negative	Immune due to hepatitis B vaccination
anti-HBc	negative	
anti-HBs	positive	
HBsAg	positive	Acutely infected
anti-HBc	positive	
IgM anti-HBc	positive	
anti-HBs	negative	
HBsAg	positive	Chronically infected
anti-HBc	positive	
IgM anti-HBc	negative	
anti-HBs	negative	
HBsAg	negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection4. Resolving acute infection
anti-HBc	positive	
anti-HBs	negative	

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefi ned time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

Appendix 8. Contraception Requirements for MEDI4736

- Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least 1 highly effective method of contraception from screening, and must agree to continue using such precautions for 90 days after the last dose of MEDI4736 monotherapy; cessation of birth control after this point should be discussed with a responsible physician. Female subjects must use a hormonal method (eg, "the pill") in addition to a barrier method (ie, male condom plus spermicide), to ensure pregnancy does not occur. Not engaging in sexual activity is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should refrain from breastfeeding and egg cell donation throughout this period.
- It is strongly recommended for the male partner of a female subject to also use a male condom plus spermicide throughout this period.
    - 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 12 months with no menses without an alternative medical cause)
    - The acceptable methods of contraception are described in Table 4. A highly effective method of contraception is defined as 1 that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Not all methods of acceptable contraception are highly effective.
- Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from Day 1 and for 90 days after the last dose of MEDI4736 monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

  It is strongly recommended for the female partner of a male subject to also use an effective method of contraception throughout this period.
- **All subjects:** Subjects should not donate blood while participating in this study and for 3 months following the last dose of study treatment.

Table 4. Effective Methods of Contraception

Barrier/Intrauterine Method	Hormonal Methods
Male or female condom with or without spermicide[a,b,c]	Implants
Cap, diaphragm, or sponge with spermicide[a,b,c]	Hormone shot or injection
Copper T intrauterine device	Combined pill
Levonorgesterel-releasing intrauterine system (eg, Mirena®)[d]	Minipillb
	Patch

a. Female partners of male subjects must use an effective method of birth control.
b. Only highly effective (<1% pregnancy rate per year) when used with additional methods of birth control.
c. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control methods.
d. This is also considered a hormonal method.

Appendix 9. Child-Pugh Score for Subjects with Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, et al. “Transection of the oesophagus for bleeding oesophageal varices”. The British journal of surgery, 1973;60:646-9.