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TITLE: Phase II Study of ABT-199 (GDC-199) in patients with relapsed or refractory Waldenström Macroglobulinemia

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Agent: BCL2 inhibitor ABT-199 (GDC-199)

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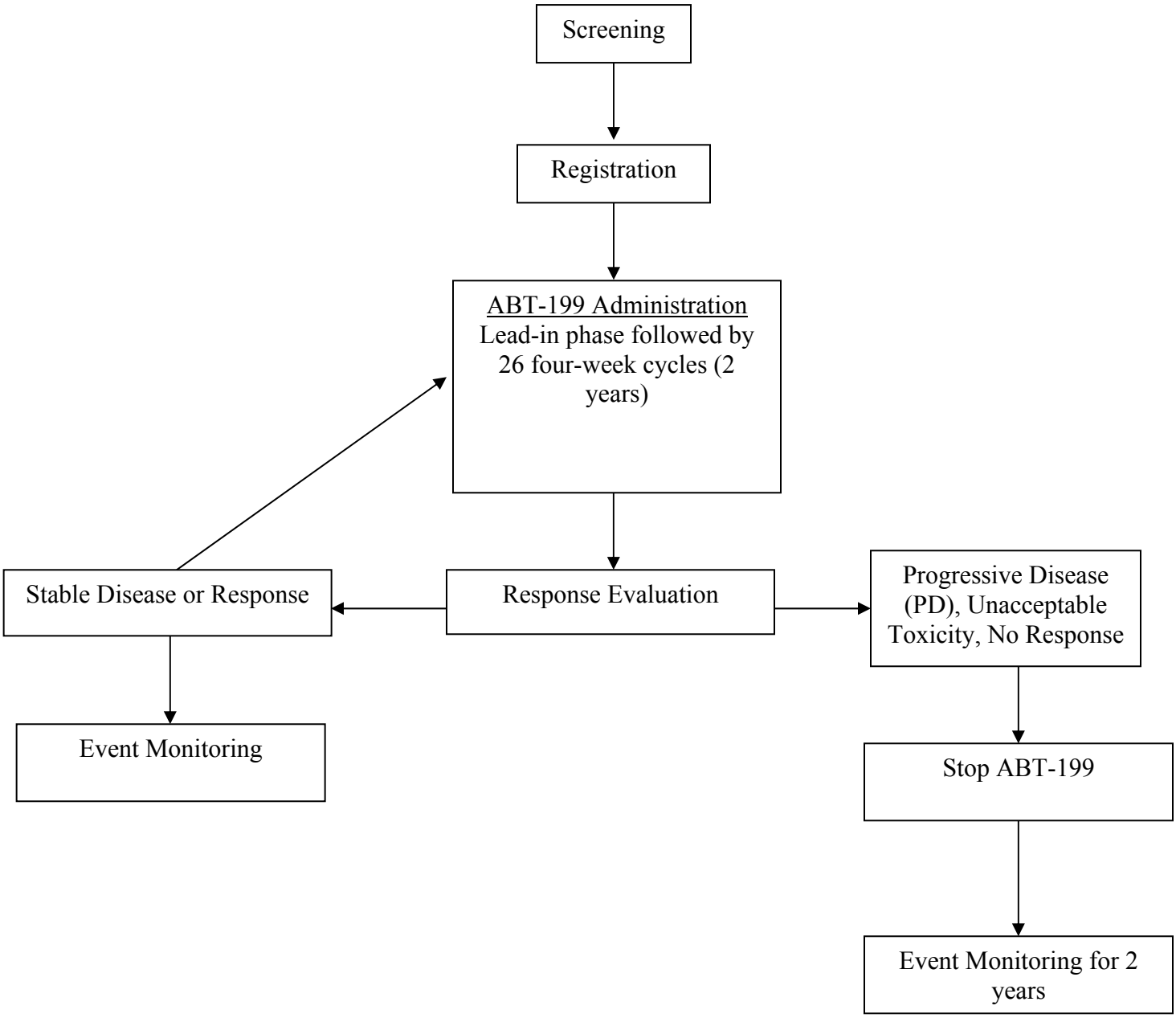
SCHEMA


Screening
Registration
ABT-199 Administration
Lead-in phase followed by 26 four-week cycles (2 years)
Response Evaluation
Stable Disease or Response
Event Monitoring
Progressive Disease (PD), Unacceptable Toxicity, No Response
Stop ABT-199
Event Monitoring for 2 years

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1. OBJECTIVES

1.1 Study Design

This is a Phase II study designed to evaluate the safety and efficacy of ABT-199 (GDC-199) in previously treated, relapsed/refractory WM patients. Treatment will be administered daily to participants with WM, and participants will receive treatment for a duration of completion of the lead-in phase to the target dose level, followed by a maximum of 2 years at this dose or until progression of disease or unacceptable toxicity. Treatment will be comprised of a lead-in phase of ABT-199 at 200 mg PO daily for 1 week, 400 mg PO daily for 1 week, and 800 mg PO daily for 2 weeks, for the first six patients enrolled (Cohort 1), followed by ABT-199 at 800 mg PO daily for 2 years following the completion of the lead-in phase. If no evidence of tumor lysis syndrome is seen, then starting with the seventh patient (Cohort 2), the lead-in phase would consist on ABT-199 at a dose of 400 mg PO daily for 1 week, and 800 mg PO daily for 3 weeks, followed by ABT-199 at 800 mg PO daily for 2 years following the completion of the lead-in phase. Therapy will continue for 2 years at the target dose provided the patients continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for subject discontinuation, with permitted dose modification for toxicity as per Table 6-1.

A Screening visit will be conducted within 30 days of Cycle 1, Day 1 of study drug administration. At the Screening visit, a medical history will be obtained and a complete physical examination will be performed including vital signs and an ECOG performance status. A bone marrow aspirate and biopsy, and CT scanning of the chest, abdomen and pelvis will be done. Bone marrow and CT scans will not be required if collected within 90 days prior to Cycle 1 Day 1 visit. Clinical laboratory tests including a complete blood count plus differential, comprehensive chemistry panel (electrolytes, BUN, creatinine, albumin, total protein, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase), magnesium, beta-2-microglobulin, serum and protein electrophoresis with quantification of immunoglobulins (IgM, IgG, IgA) and immunofixation studies, Von Willebrands factor, HIV, HBsAg, HBsAb, HBcAb and HCV antibody. Serum pregnancy tests for women of childbearing potential will also be performed at the Screening visit. Cryoglobulins and cold agglutinins will be obtained if clinically indicated. Coagulation studies (PT, PTT, PT-INR) and tumor lysis laboratories (calcium, phosphorus, LDH, and uric acid) will also be performed at baseline.

Participants who meet the eligibility requirements as assessed at the Screening visit will be enrolled in the study and initiated on study drug. Participants will be evaluated for development of tumor lysis syndrome (TLS) on Days 1 and 2 of dose escalation days during the lead-in phase. TLS, however, is an extremely rare occurrence in patients with WM. To err in the side of safety, all patients will receive allopurinol 300 mg PO once daily starting 72 hours prior to first dose of ABT-199 and continuing at least throughout the lead-in (Cycle 1) period. All patients will be encouraged to drink 2 L of fluid the day before starting ABT-199. Patients in whom oral intake is inadequate, 1 L of 0.9% normal saline will be administered IV prior to first dose of ABT-199 and prior to each dose escalation of ABT-199. All patients will be monitored for TLS at 8 hours and 24 hours after starting ABT-199, and at each dose escalation at least until week 2, as needed to reach the maximum dose of 800 mg PO daily. Patients with laboratory or clinical evidence of

TLS will be hospitalized for further management. The inpatient management of TLS, frequency of monitoring and duration of hospitalization will be decided by the investigator, aided by the guidelines in Appendix B (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]). In patients who developed TLS, hospitalization for at least 24 hours will be needed for subsequent dose escalations. Patients will be evaluated for response on the first day of each cycle (4 weeks ± 1 week) at cycle 2, and 3 and thereafter every 3 cycles (12 weeks ± 2 weeks) for the duration of therapy. Participants will be eligible to continue therapy for 2 years at the target dose following the completion of the lead-in phase, provided the patients continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for subject discontinuation.

Response criteria updated at the Sixth International Workshop on Waldenström macroglobulinemia (Owen 2013) will be used to assess response, stable disease, and progressive disease. Response outcomes to be determined will include: Best overall response rate (including minor, partial, very good partial and complete response rate) and major response rate (including partial, very good partial and complete response rate), landmark analysis for 2 and 4-year overall survival (OS), progression-free survival (PFS) and median duration of response (DOR). The duration of therapy will depend on individual response, evidence of disease progression and tolerance of the drug. If at the end of study therapy, it is deemed that WM patients derive benefit from ABT-199, AbbVie will work with the investigator to evaluate options for continuation of ABT-199. If ABT-199 were to become commercially available, then patients still enrolled in the study will have the option of receiving ABT-199 via prescription coverage. Follow-up will continue for 2 years or until new therapy after patients had stopped taking ABT-199 for any reason, except death.

1.2 Primary Objectives

- To assess the best overall response rate (ORR) of ABT-199 in symptomatic WM patients with relapsed/refractory disease.

1.3 Secondary Objectives

- To assess the safety and tolerability of ABT-199 in symptomatic WM patients with relapsed/refractory disease.
- To evaluate the rate of CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) and progressive disease (PD).
- To evaluate the 2-year and 4-years median OS, median PFS and median duration of response (DOR).
- To evaluate the toxicity profile of ABT-199 in patients with relapsed/refractory WM
- To evaluate the association between presence of MYD88 and CXCR4 mutations and response to ABT-199

2. BACKGROUND

2.1 Study Disease(s)

WM is a rare B-cell lymphoproliferative disorder characterized by the uncontrolled accumulation of IgM-producing lymphoplasmacytic cells. Such malignant cells accumulate in the bone marrow, liver, spleen and lymph nodes. WM is diagnosed by the presence of lymphoplasmacytic cells in the bone marrow and an IgM monoclonal spike (M-spike) identified in a serum protein electrophoresis (SPEP) (Swerdlow 2002). The incidence of WM in the United States (US) is approximately 0.3 per 100,000 persons per year accounting for approximately 1000 new cases per year (Sekhar 2012), although this is likely to be an underestimation. The clinical course of WM is variable and although patients might experience an overall survival (OS) measured in decades (Castillo 2014), WM remains incurable with current therapeutic regimens (Treon 2009). Hence, the disease course is characterized by continual relapses, each harder to treat than the previous one. Additionally, many of the disabling symptoms associated with the disease, such as hyperviscosity, fatigue, anemia or neuropathy, can be exacerbated by therapy. Rituximab can induce disabling IgM flare (Treon 2002), alkylating agents and nucleoside analogs can be associated with the development of secondary MDS/AML (Leleu 2009), bortezomib can cause high rates of peripheral neuropathy (Treon 2009), and carfilzomib can induce severe hypogammaglobulinemia (Treon 2014). Hence, the careful evaluation of agents with novel mechanisms of action is needed to improve the quality of life (QOL), and response and survival rates in patients with WM.

Recently, our group identified a recurrent mutation in the MYD88 gene (MYD88 L265P), which is seen in over 90% of cases with WM (Treon 2012). The occurrence of this mutation in WM has since been validated in several independent cohorts. In contrast, the MYD88 L265P gene mutation was not detected in patients with IgM myeloma, and was detected in less than 10% of patients with marginal zone lymphoma. The high specificity and sensitivity of the MYD88 L265P gene mutation has obvious diagnostic implications in patients in whom a diagnosis of WM is suspected but uncertain. The MYD88 L265P gene mutation has shown to support growth and survival of WM cells in several studies. A knockdown model of MYD88 showed decreased survival of MYD88 L265P expressing WM cells, whereas survival was more enhanced by knock-in of mutant *versus* wild-type MYD88. MYD88 acts as an adaptor molecule in toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling. Following stimulation of TLR or IL-1R, MYD88 is recruited to the activated receptor complex as a homodimer which complexes with IL-1R-associated kinase 4 (IRAK4) and subsequently activates IRAK1 and IRAK2. IRAK1 activation then leads to NF-κB activation via IκBα phosphorylation. Recently, a study has shown that MYD88 L265P also activates the Bruton's Tyrosine Kinase (BTK) pathway (Yang 2013). In this pre-clinical study, the activation of BTK by MYD88 could be abrogated by the use of BTK kinase inhibitors. Clinically, the use of the oral BTK inhibitor ibrutinib has shown to be effective in patients with WM (Treon 2013). A phase II study on 63 patients with relapsed/refractory WM was performed evaluating ibrutinib at a dose of 420 mg PO once daily. The ORR was approximately 80% with relatively well-tolerated AE profile. The median time to response (IgM level decrease by at least 25% of baseline) was 4 weeks. At a median follow-up of 18 months, 80% of patients continue on ibrutinib.

Another study from our group reported the occurrence of recurrent somatic CXCR4 gene mutations in approximately 30% of WM patients (Hunter 2013). The somatic mutations occur in the C-terminal domain, and are similar to those observed in patients with WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome. These mutations regulate

signaling of CXCR4 by its ligand SDF-1a. In WM patients, two classes of CXCR4 mutations occur: non-sense ($CXCR4^{WHIM/NS}$) and frameshift ($CXCR4^{WHIM/FS}$) mutations. Non-sense and frameshift mutations are almost equally divided among WM patients, and over 30 different types of CXCR4 mutations have been identified. Preclinical studies with the most common CXCR4 S338X mutation in WM have shown sustained signaling of AKT, ERK and BTK following SDF-1a binding in comparison with wild-type CXCR4, as well increased cell growth and survival of WM cells. CXCR4 mutations have been associated with resistance to ibrutinib (Cao 2014). In the phase II study of ibrutinib in relapsed/refractory WM patients, patients carrying CXCR4 mutations had lower rates of response and lower depth of response to ibrutinib (Treon 2014). Hence, there is an unmet need for more effective, better-tolerated drugs for patients with WM.

2.2 IND Agent ABT-199

ABT-199 (GDC-0199) is a novel, orally bioavailable, small-molecule B-cell lymphoma-2 (Bcl-2) family inhibitor in the biarylacylsulfonamide chemical class. ABT-199 binds with high affinity (inhibition constant [Ki] < 0.010 nM) to antiapoptotic protein Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins, like Bcl-XL and Bcl-w (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).

Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance, as well as autoimmunity. Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies; antagonism of the action of these proteins may enhance response to therapy and overcome resistance, and thus, these proteins are compelling targets for anti-tumor therapy (Fesik 2005). Currently, AbbVie, Inc. and Genentech/Roche are investigating ABT-199 in both oncology and immunology studies.

Pre-clinical studies

In vitro, ABT-199 demonstrated cell killing activity against patient-derived chronic lymphocytic leukemia (CLL) and acute myeloid leukemia (AML) cells and a variety of lymphoma and leukemia cell lines, including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B –cell lymphomas (DLBCLs), AMLs, and multiple myeloma (MM). ABT-199 was especially potent against non-Hodgkin lymphoma (NHL) cell lines expressing high levels of Bcl-2.

ABT-199 inhibits subcutaneous xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL), NHL, and AML, and is highly efficacious using various doses and combined with other regimens. The drug is also active in a model of disseminated ALL and AML. ABT-199 enhanced the activity of a broad variety of chemotherapeutic agents in other human hematological models. Specifically, ABT-199 enhances the efficacy of bendamustine and rituximab (BR) in models of MCL and DLBCL. Furthermore, ABT-199 demonstrated potential to enhance the efficacy of bortezomib in multiple models of MM.

Pre-clinical safety

ABT-199 was tested in a battery of safety pharmacology assays and produced no effects in

central nervous system (CNS)/neurobehavioral, or respiratory studies in mice at oral doses up to 600 mg/kg. In dogs, mild reductions in cardiac contractility and cardiac output were observed at plasma concentrations of ≥ 16 μg/mL; concentrations greater than the concentration of ABT-199 in humans (3.39 μg/mL at the 900 mg dose). However, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed in dogs at a maximum drug concentration of 46 μg/mL.

Pre-clinical pharmacokinetics

ABT-199 exhibited moderate permeability in the Caco-2 assay. In rats, ABT-199 was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. ABT-199 showed moderate in vitro metabolic stability in hepatic systems across species tested, with the exception of dog hepatocytes, where stability was low to moderate. In rat, 14.3% of the dose was recovered as parent drug after 48 hours post-dose, while 76.9% of the dose was excreted as metabolites in bile. Profiles in bile indicated that metabolism was the major clearance mechanism, while biliary excretion of parent drug played a secondary role in drug elimination. Biotransformation of [3H]ABT-199 proceeded via a combination of oxidation and conjugation.

ABT-199 was not a potent inhibitor of the cytochrome P450 enzymes CYP3A4, CYP1A2, CYP2B6, or CYP2D6 (50% inhibition constant [IC50] > 30 μM), but was a weak inhibitor of CYP2C19 (IC50 = 23.9 μM), a moderate inhibitor of CYP2C8 (IC50 = 4.4 μM), and a potent inhibitor of CYP2C9 (IC50 = 0.37 μM). At concentrations of 1, 3, and 10 μM, ABT-199 did not induce CYP3A4 or CYP1A2 expression in vitro. ABT-199 was metabolized by CYP3A4; thus, its exposure could be affected when potent inhibitors or inducers of CYP3A4 are coadministered.

Pre-clinical toxicology

The primary toxicities associated with ABT-199 administration included effects on the hematologic system (decreased lymphocytes and erythrocytes) in mice and dogs; the male dog reproductive system (testicular germ cell depletion); and embryofetal toxicity in mice. In mice and dogs, ABT-199 produced robust decreases in lymphocytes in the peripheral blood (up to 75% in mice and up to 80% in dogs) and in lymphoid tissues. These findings are consistent with the expected pharmacologic effects of selective Bcl-2 inhibition. In dogs, the recovery of lymphocyte counts (total lymphocytes, CD4+ and CD8+ T cells and mature B cells) was prolonged, requiring up to 18 weeks after completion of 2 weeks of dosing. B cells were the most sensitive lymphocyte subtype based on the magnitude of decrease and/or the length of time required for recovery. ABT-199 effects on red blood cell mass parameters principally consisted of dose-related decreases in hematocrit and hemoglobin in mice and dogs; these effects were adverse only at the highest dosages in the 4-week mouse and dog studies and were reversible. In dogs, ABT-199 produced adverse, non-reversible, non-dose-related microscopic findings of testicular germ cell depletion at all doses tested; there were no testicular effects in mice.

Decreases of lymphocytes in lymphoid tissue were reversible in mice and reversible to partially reversible in dogs. ABT-199 resulted in increased post-implantation loss, and decreased fetal body weights were observed in the mouse embryofetal development study at the highest dosage

administered (150 mg/kg/day); the no-observed-adverse-effect level (NOAEL) was defined at the mid-dose of 50 mg/kg/day. ABT-199 was not teratogenic, and there were no other effects on development or fertility. Other effects of ABT-199 included loss of hair pigmentation in dogs, single cell necrosis in various epithelial tissues in dogs (e.g., gallbladder) that was of minimal magnitude and produced no loss of mucosal integrity, and increased pigment in Kupffer cells or macrophages in the liver and gallbladder of dogs. None of the effects were considered to be adverse, and all were reversible with the exception of hair coat discoloration. There was no evidence of in vitro or in vivo genetic toxicity of ABT-199.

Clinical experience with ABT-199

Multiple ongoing Phase I/II AbbVie, Inc. and Genentech/Roche clinical studies are evaluating safety, tolerability, pharmacokinetics, and efficacy of ABT-199 as monotherapy or in combination with other therapies (rituximab, BR, bortezomib plus dexamethasone, or obinutuzumab) in subjects with hematologic malignancies.

A drug-drug interaction (DDI) study evaluating the interaction of ABT-199 and ketoconazole is ongoing. Additionally, a Phase 3 study of ABT-199 plus rituximab compared with BR in subjects with CLL has been initiated.

Summary of Safety Data

A total of 257 subjects were enrolled and had data available in AbbVie, Inc. studies as of 03 February 2014. Of these 257 subjects, 150 subjects had CLL/SLL, 82 subjects had NHL, 12 subjects had MM, and 13 had AML. A total of 192 received the drug as monotherapy and 65 received the drug in combination with other therapies. Among the subjects who received ABT-199, the median duration of drug administration was 126 days (range: 1 to 837 days), with 100 subjects having received 180 days or longer of therapy. Additionally, 10 subjects were enrolled and had data available in Genentech/Roche oncology studies as of 03 February 2014. Eight subjects with CLL received ABT-199 + obinutuzumab in Study GP28331, and were on study for a median of 61 days (range: 3 to 195 days). Two subjects received ABT-199 + BR in Study GO28440, and have been on study for 3 and 18 days, respectively.

Based on nonclinical and clinical data available with ABT-199 administration the identified and potential risks are nausea, diarrhea, TLS, hematological effects (including neutropenia/febrile neutropenia, anemia, thrombocytopenia, and lymphopenia), serious and/or opportunistic infections, and decreased spermatogenesis. In addition, as ABT-199 is being evaluated in subjects with relapsed/refractory disease and has potential immunomodulatory properties, the risks of RS and secondary primary malignancies are closely monitored.

Clinical Pharmacokinetic and Pharmacodynamic Data

Preliminary pharmacokinetic data with ABT-199 are available from ongoing oncology Studies M12-175, M12-630, M13-365, and M13-367, and GP28331 in subjects with hematologic malignancies, and the ongoing immunology study in subjects with SLE (Study M13-093). The ABT-199 formulation currently used in clinical studies is a tablet formulation with strengths

of 10, 50, and 100 mg. The tablet formulation was orally administered after a low-fat meal. Food increased the bioavailability of ABT-199 by 3- to 4-fold. Preliminary pharmacokinetic results indicated that the absorption of ABT-199 after the oral dosing was relatively slow. ABT-199 plasma concentrations peaked at approximately 6 hours after dosing. The mean harmonic terminal phase elimination half-life of ABT-199 was approximately 17 hours and the mean oral clearance was approximately 13 L/hr after a single dose. Preliminary data did not suggest apparent pharmacokinetics differences among subjects with CLL/small lymphocytic leukemia (SLL), NHL, multiple myeloma (MM), or SLE. The combined data from subjects with CLL/SLL and NHL suggested that ABT-199 exposure was approximately dose proportional across the 150 to 1200 mg dose levels at steady state. Coadministration of bendamustine and rituximab did not show apparent impact on ABT-199 pharmacokinetics. On the basis of limited preliminary data from Cohort 1 of Study GP28331 (ABT-199 administered alone and in combination with obinutuzumab), obinutuzumab did not appear to affect ABT-199 exposure.

Clinical Efficacy as monotherapy

Data from a phase I study in patients with relapsed/refractory CLL has been recently presented at the 2014 ASCO Annual Meeting (Seymour 2014). The data cut-off date was December 4, 2014. From the 84 patients in the study, 23 (27%) had del(17p) and 48 (57%) were refractory to fludarabine. The ORR was 79% with a CR/CRi rate of 22% with a median DOR of 21 months. At 12 months, 91% of patients in CR and 65% in PR remained progression free. The ORR was 78% in del(17p) patients and 79% in fludarabine-refractory. The most common AEs were diarrhea (37%), nausea (36%), neutropenia (35%) and anemia (8%). TLS was seen in 8%, including one grade 5 AE. Febrile neutropenia, thrombocytopenia, hyperglycemia and hypokalemia were seen in 6% of patients each.

Also, results from a phase I study in patients with relapsed/refractory NHL were presented (Davids 2014). So far, 44 patient have been enrolled, 15 (35%) with MCL, 11 (26%) with FL, 10 (23%) with DLBCL, 4 (9%) with WM, 2 (5%) with MZL, 1 (2%) with PMBCL, and 1 (2%) with MM. The ORR was 48%, 9/12 MCL (1 CR), 3/11 FL, 3/9 DLBCL (1 CR), 3/4 WM (1 CR), 1/2 MZL, 0/1 PMBCL, and 0/1 MM. All the responses in DLBCL and FL patients were seen at doses >600 mg. The most common AEs were nausea (34%), URI (27%), diarrhea (25%) and fatigue (21%). Also, Grade 3 or 4 seen were anemia (14%), neutropenia (11%) and thrombocytopenia (9%). Laboratory TLS was seen in 1 patients with MCL and 1 patients with DLBCL.

2.3 Rationale

Overexpression of Bcl-2 in WM. The B-cell lymphoma-2 (BCL-2) family of proteins is central to the regulation of apoptosis. Altered responses to normal apoptotic signals are one of the hallmarks of cancer and they are connected to defects in the apoptotic machinery in cancer cells. Apoptosis occurs via activation of two different pathways, the extrinsic pathway, triggered by the activation of the cell surface death receptors, and the intrinsic pathway, followed by the perturbation of mitochondrial membrane integrity. Studies have shown that the intrinsic pathway is tightly controlled by the interactions between the pro- and anti-apoptotic BCL-2 family proteins (Bajwa 2012). Twenty-five known members of the BCL-2 protein family can be

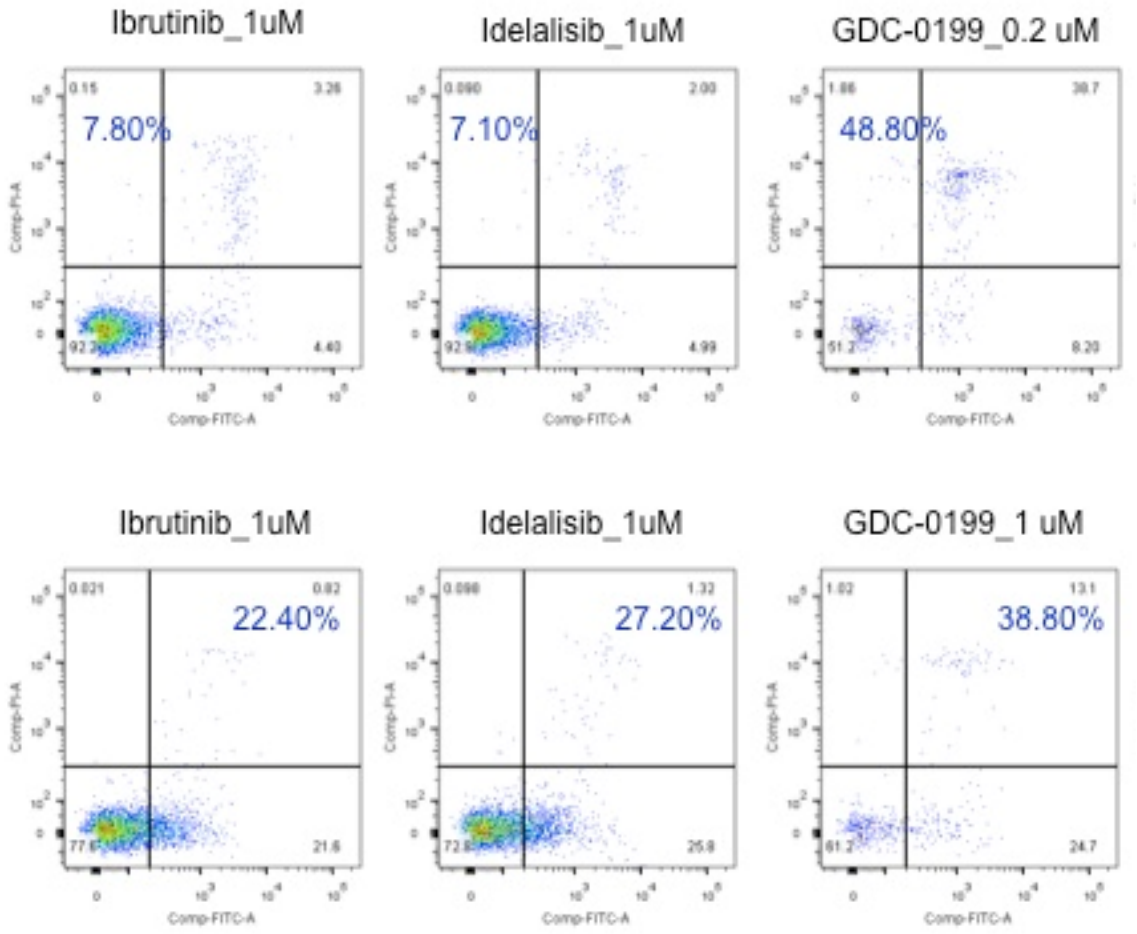
grouped functionally according to their pro- and anti-apoptotic effects, as well as structurally according to the BCL-2 homology (BH) regions they contain. The six known anti-apoptotic family members, BCL-2, Bcl-x_L, Mcl-1, Bcl-w, Bcl-b and A1, contain four BH domains (BH1-4) and a transmembrane domain (TM). Pro-apoptotic proteins are subdivided into two classes: multi-domain members, such as Bax, Bak and Bok, which contain and share homology in the BH1, BH2, BH3 and BH4 domains and BH3-only proteins, including Bad, Bim, Puma, Bid, Bik, Noxa, Hrk and Bmf, which show homology only in the BH3 domain.

By gene expression analysis, we investigated differences in transcriptional regulation of CD19 and CD138 selected cells representing the B-cell and plasma cell compartments, respectively, versus similar healthy donor derived bone marrow cells. Samples from 30 untreated WM patients were compared to those of 10 healthy donors (Hatjiharissi 2007). These studies demonstrated that Bcl-2 was overexpressed in both B-cell and plasma cell compartments in WM patients in comparison to healthy donors. By flow cytometric analysis, the overexpression of Bcl-2 protein has also been confirmed in a Spanish study on 60 cases meeting pathologic criteria for WM (San Miguel 2003). Enhanced Bcl-2 expression has also been linked to familial predisposition to WM in an Icelandic study (Ogmundsdottir 2009), while use of Bcl-2 inhibitors have shown preclinical (oblimersen, AT-101) as well as clinical activity (oblimersen) in WM (Gertz 2005; Paulus 2014).

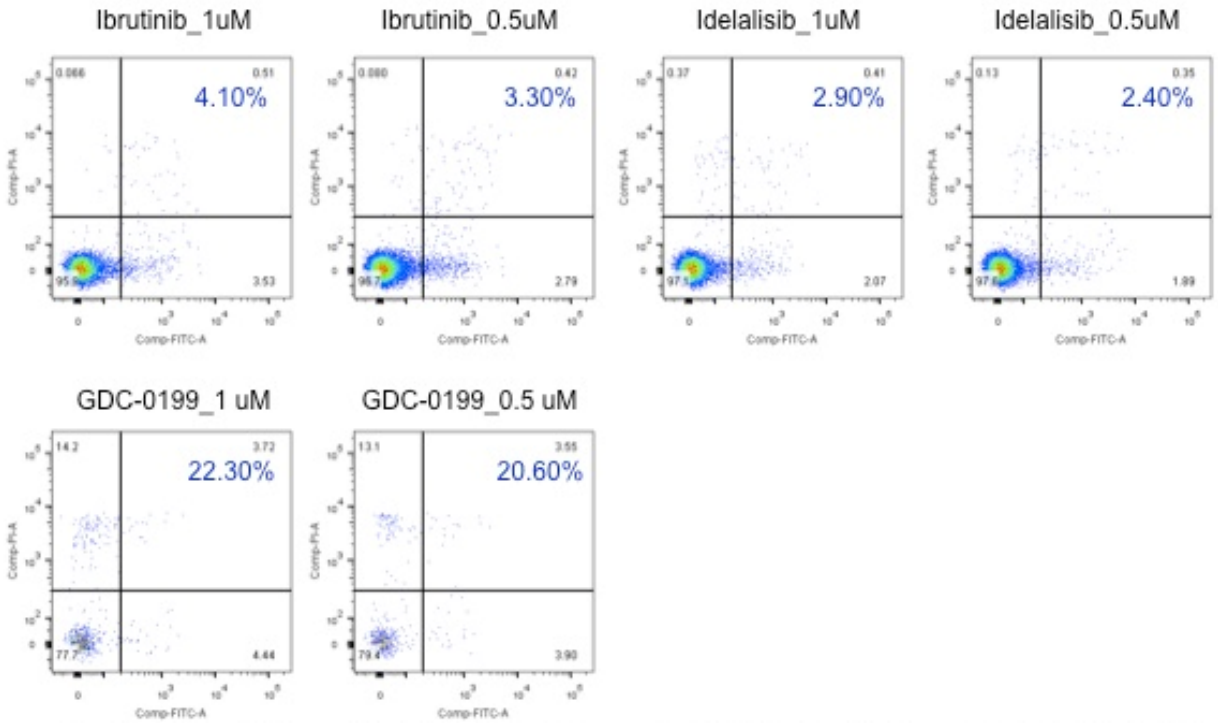
Previous BCL-2 inhibitors (ABT-263), although active in CLL and NHL, caused dose-dependent thrombocytopenia that limited further clinical development. To circumvent this challenge, a unique BCL-2–small molecule cocrystal structure was used to design ABT-199, a first-in-class BCL-2–selective inhibitor that causes substantially less platelet killing *ex vivo* and *in vivo* as compared to ABT-263. In addition to showing preclinical efficacy in BCL-2–dependent cell lines and tumor xenograft models, ABT-199 demonstrated immediate activity in patients with refractory lymphoid malignancies while causing only minor changes in platelet counts (Souers 2013).

Preclinical evidence of ABT-199 activity in WM cell lines. In our laboratory, we evaluated the pro-apoptotic effects of ABT-199 using Annexin V BCWM.1 and MWCL-1 (unpublished data). The treatment effects were evaluated following 18 hours of culture with ABT-199 or the BTK inhibitor ibrutinib at 5 uM. As a reference, ibrutinib has been shown to be highly effective in patients with relapsed/refractory WM, showing an ORR of over 80%. We observed that ABT-199 was able to induce a higher level of apoptosis than ibrutinib in both cells lines (see figures). Interestingly, ABT-199 not only induced higher apoptosis in CXCR4-mutated cell lines but the level of apoptosis appeared similar in wild-type as well as cells engineered to express the CXCR4 S338X non-sense mutation. Finally, the combination of ABT-199 and ibrutinib showed greatly enhanced cytotoxicity in both BCWM.1 and MWCL-1 wild-type and CXCR4 S338X expressing cells, an important finding given that CXCR4 S338X mutations confer resistance against ibrutinib.

Preclinical evidence of ABT-199 activity in primary WM cells. We have conducted similar apoptotic essays using ABT-199, ibrutinib and the phosphatidylinositol 3-kinase inhibitor idelalisib in primary cells from WM patients (unpublished data). We observed that ABT-199 at concentrations of 0.2 uM and 1 uM induced significantly higher levels of apoptosis than ibrutinib and idelalisib at concentrations of 1 uM.



In a separate experiment, we evaluated the apoptotic effect of ABT-199, ibrutinib and idelalisib at concentrations of 0.5 uM and 1 uM.



Clinical evidence of ABT-199 activity in WM patients. Davids and colleagues presented updated results from a phase I study using ABT-199 in patients with relapsed/refractory NHL [25]. From the 4 patients with WM enrolled, 3 responded for an ORR of 75%, including 1 VGPR.

Hypothesis

Single agent ABT-199 (GDC-199) is safe and is associated with a high overall response rate in patients with relapsed/refractory WM.

2.4 Correlative Studies Background

MYD88 L265P is a recently identified somatic mutation present in >90% of WM patients but in <5% of patients with other related processes such as CLL or MZL with plasmacytic differentiation or IgM myeloma (Treon 2012). Many groups have now validated the presence of this somatic mutation in WM patients. MYD88 L265P supports growth and survival of WM cells through both IRAK1 and IRAK4 (Treon 2012) as well as by activation of Bruton tyrosine kinase (BTK) (Yang 2013). Based on these findings, we conducted a clinical trial using the BTK inhibitor ibrutinib in 63 patients with relapsed/refractory WM (Treon 2013). In this study, ibrutinib showed to be safe and effective. Median hemoglobin improved from 10.5 g/dl to 12.6 g/dl and IgM decreased from 3610 mg/dl to 1340 mg/dl. Bone marrow involvement decreased from 70% to 45% with a best ORR of 81% and a major response rate of 57%. The major response rate was 77% for patients with wild-type CXCR4 vs. 30% in those with WHIM-like CXCR4 mutations. Decreases in serum IgM as well as improvements in hemoglobin were greater in patients with wild-type CXCR4.

In recent studies, the MYD88 and CXCR4 mutational status are predictive of clinical status, response to therapy and survival outcomes (Cao 2013, Treon 2013, Treon 2014). Activating

MYD88 as well as nonsense and frameshift WHIM-like CXCR4 somatic mutations are common in Waldenström macroglobulinemia. CXCR4 nonsense mutations are present in aggressive cases including hyperviscosity syndrome, and MYD88 status is a determinant of survival. The MYD88 L265P mutational analysis by allele-specific PCR and CXCR4 mutational analysis by Sanger sequencing will be performed by the Bing Center for Waldenström Macroglobulinemia in Boston, MA.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Clinicopathological diagnosis of Waldenstrom's Macroglobulinemia and meeting criteria for treatment using consensus panel criteria from the Second International Workshop on Waldenstrom's macroglobulinemia (Owen 2003; Kyle 2003).

3.1.2 Measurable disease, defined as presence of serum immunoglobulin M (IgM) with a minimum IgM level of > 2 times the upper limit of normal of each institution is required.

3.1.3 Have received at least one prior therapy for WM.

3.1.4 Age ≥ 18 years.

3.1.5 ECOG performance status ≤2 (see Appendix A).

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

- Absolute neutrophil count ≥ 1,000/mm^3
- Platelets ≥ 50,000/mm^3
- Hemoglobin ≥ 8 g/dL
- Total bilirubin ≤ 1.5 X ULN
- AST (SGOT) and ALT (SGPT) ≤ 2.5X the institutional upper limit of normal
- Creatinine clearance ≥50 ml/min

3.1.7 Not on any active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

3.1.8 Females of childbearing potential (FCBP) must agree to use two reliable forms of contraception simultaneously or have or will have complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) while participating in the study; and 2) for at least 28 days after discontinuation from the study. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. FCBP must be referred to a qualified provider of contraceptive methods if needed.

3.1.9 Able to adhere to the study visit schedule and other protocol requirements.

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

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

3.2.1 Any serious medical condition, laboratory abnormality, uncontrolled intercurrent illness, or psychiatric illness/social condition that would prevent the participant from signing the informed consent form.

3.2.2 Concurrent use of any other anti-cancer agents or treatments or any other study agents.

3.2.3 Concurrent administration of medications or foods that are moderate or strong inhibitors or inducers of CYP3A within 7 days prior to first dose of study drug.

3.2.4 Prior exposure to ABT-199 or BCL2 inhibitors.

3.2.5 Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, ECG finding, or laboratory abnormality that, in the investigator's opinion, could affect the safety of the patient, including symptomatic hyperviscosity; alter the absorption, distribution, metabolism or excretion of ABT-199; or impair the assessment of study results.

3.2.6 Grade > 2 toxicity (other than alopecia) continuing from prior anti-cancer therapy.

3.2.7 Known CNS lymphoma.

3.2.8 Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening.

3.2.9 New York Heart Association classification III or IV heart failure.

3.2.10 Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.

3.2.11 Known history of Human Immunodeficiency Virus (HIV), chronic hepatitis B virus (HBV), or hepatitis C (HCV) requiring treatment. Note: Subjects with serologic evidence of prior vaccination to HBV (i.e., HBs Ag-, anti-HBs+ and anti-HBc-) and positive anti-HBc from IVIG may participate

3.2.12 Lactating or pregnant women.

3.2.13 Inability to swallow tablets.

3.2.14 History of non-compliance to medical regimens.

3.2.15 Unwilling or unable to comply with the protocol.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator. All sites should call the Project Manager Kirsten Meid at 617-632-5598 to verify dose level availabilities.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed [617-632-6752] or e-mailed [kirsten_meid@dfci.harvard.edu] to the Project Manager:

- Copy of serum protein electropheresis, CBC, COMP, CT C/A/P, bone marrow biopsy
- Screening visit note
- Signed participant consent form
- HIPAA authorization form
- Eligibility Checklist

The Eligibility Checklist should be filled out by a clinical study staff member and the "Screening Staff" section must be signed by them. Study staff at the Coordinating Center will review the eligibility documentation and sign as the "Enrollment Monitor."
The research nurse or data manager at the participating site will then call *[617-632-5598* or e-mail *[kirsten_meid@dfci.harvard.edu]* the Project Manager to verify eligibility. To complete the

registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101B) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Treatment Regimen

ABT199 will be administered daily, with 28 consecutive days defined as a treatment cycle for cycles 2-26 for a maximum for 25 cycles once the target dose is reached. Treatment will be administered on an outpatient basis, except as specified below. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 Pre-Treatment Criteria

C1D1 results do not need to meet eligibility parameters. Day 1 chemistry and hematology laboratories must be reviewed prior to treatment.
Participants must meet the following criteria on Day 1 of cycles with clinic visits (i.e. 1, 2, 3, 6, 9, etc.):

- No grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal thearpy)
- No grade 4 or unmanageable nonhematologic grade 3 toxicities
- Neutrophil count >/=500/ mm^3 (growth factor permitted)
- In subjects without baseline thrombocytopenia:
    - Platelet count >/= 50,000/ mm^3 in the presence of bleeding
    - Platelet count >/= 25,000 mm^3 without bleeding
- In subjects with baseline thrombocytopenia:
    - Platelet count decrease <75% or >/= 20,000/ mm^3, whichever is higher without bleeding
    - Platelet count decrease <50% in the presence of bleeding

5.3 Agent Administration

Cycle 1 of treatment will consist of the lead-in phase of drug escalation for all patients. Cycle 1 will last for a minimum of 4 weeks (+ 2 days) and may continue until patients reach the maximum target dose level for 2 consecutive weeks for those needing dose adjustments during escalation. For the first six patients (Cohort 1), the lead-in phase will consist of ABT-199 (GDC-199) administered at a dose of 200 mg (2 tablets) PO once daily for 7 (+2) days, followed by 400

mg (4 tablets) PO once daily for 7 (+2) days, followed by 800 mg (8 tablets) PO once daily until disease progression, unacceptable toxicity, or for total drug study duration of 26 cycles (2 years), whichever comes first. If no evidence of TLS is seen in the first six patients, for the remaining patients (Cohort 2) the lead-in phase will consist of ABT-199 (GDC-199) administered at a dose of 400 mg (4 tablets) PO once daily for 7 (+2) days followed by 800 mg (8 tablets) PO once daily until disease progression or unacceptable toxicity for total drug study duration of 26 cycles (2 years), whichever comes first. Dose reductions due to toxicity will be permitted on information seen in Table 6-1.

The study drug ABT-199 will be administered at the DFCI, or participating site, infusion room on day 1 of study and at first dose of each dose escalation (C1D1, C1D8, and C1D15 for the first 6 patients, C1D1 and C1D8 for all other patients if no TLS is seen in the first 6) until a dose of 800 mg PO daily is reached. Otherwise, ABT-199 will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken. Participants will be instructed to take the study drug at approximately the same time each day. Participants will also be instructed on how to complete the diary. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the patient should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit; this must be documented in the study diary. Furthermore, they will be instructed to call the PI or research nurse if vomiting occurs. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the participant, and all dose changes during the study must be recorded.

One cycle of ABT-199 is once daily, oral administration for 4 weeks ± 1 week. Prescriptions for ABT-199 will be written for daily administration for 1 cycle for participants in cycles 1 and 2, and will be written for daily administration for 12 weeks ± 2 weeks for participants being seen every 12 weeks starting on Cycle 3 Day 1. For patients who have Cycle 1 extended due to difficulties reaching the maximum target dose during dose escalation, a new script may be written mid-cycle. Drug accountability will be done at each study visit; unused drug and diaries will be collected from the participant, unused drug will be counted and returned to the pharmacy to be destroyed. A new prescription for either one cycle or three cycles, as detailed above, will be filled by the participant, and they will be given a new diary.

Medication labels will comply with US legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label.

Tumor Lysis Syndrome Prophylaxis *(Refer to Appendix B for Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS & refer to Appendix C for Definition of Laboratory and Clinical TLS))*
First Dose of ABT-199

Tumor lysis syndrome prophylaxis must be initiated in all subjects irrespective of their TLS risk category prior to the first dose of ABT-199. TLS prophylaxis includes:

- An oral agent to reduce the uric acid level (e.g., allopurinol) to be initiated at least 72 hours prior to dosing. Treatment should be continued for at least the lead-in period (Cycle 1) based on the ongoing risk of TLS development. Subjects allergic to allopurinol must use another uric acid reducer.
- Oral hydration consisting of fluid intake of 2 L per day starting at least 24 hours prior to the start of treatment for all subjects prior to first dose and continued for at least 24 hours after dosing and all of the chemistries laboratory values remain within ULN. Oral hydration is recommended beyond 24 hours post-dose for subjects who demonstrate any laboratory changes.
- Patients who are unable to maintain such oral hydration will receive IV hydration of 1 L in the outpatient setting on Day 1 in addition to oral hydration. In subjects for whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be collected and sent to local laboratory within 72 hours prior to the first dose of ABT-199. These laboratory values must be reviewed by the investigator. The investigator's decision to proceed with ABT-199 treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests must be performed by local laboratory STAT at 0 hour (pre-dose, within 4 hours before ABT-199 administration), 8 hours post-dose (+/-30 minutes), and 24 hours after the first dose of ABT-199 at 400 mg. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post ABT-199 administration. Results from pre-dose laboratory values are not required to be available prior to initiating ABT-199 treatment. Subjects must remain at the hospital, or clinic, until the 8-hour laboratory values have been reviewed by the investigator.
- Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see Appendix B, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for procedures to follow. Additional laboratory assessments may be performed per investigator discretion.
- All 24-hour post-dose laboratory assessments (Chemistry and Hematology) may be taken within a +/- 1 hour window, if necessary.

First Dose of ABT-199 at Dose Escalation to 400 mg and 800 mg

All subjects, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of ABT-199:

- Continue administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 2 L/day starting at least 24 hours prior to each dose escalation and continued for at least 24 hours after the dose. In subjects who are unable to maintain such oral hydration, IV hydration with 1 L of 0.9% normal saline will be given in the outpatient setting on the day of dose escalation. In subjects for whom volume overload is considered a significant risk, hospitalization should be considered.

- For subjects who receive their subsequent dose escalations in the outpatient in clinic setting, Chemistry laboratory tests will be performed by the investigative site laboratory at 0 hour (pre-dose, within 4 hours before ABT-199 administration), 8 hours post-dose (+/-30 minutes) and 24 hours post dose administration. Hematology laboratory tests should be performed at 0 hour (pre-dose, within 4 hours before ABT-199 administration. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post ABT-199 administration.
- Subjects must remain at the hospital, or clinic, until the 8-hour laboratory values have been reviewed by the investigator.
- Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Additional laboratory assessments may be performed per investigator discretion.
- All 24-hour post-dose laboratory assessments (Chemistry and Hematology) may be taken within a +/- 1 hour window, if necessary.
- For subjects who are hospitalized during subsequent dose escalations, Chemistry and Hematology laboratory tests will be collected and sent to local laboratories upon admission. Chemistry tests will be performed by local laboratory STAT at 0 hour (pre-dose, within 4 hours before ABT-199 administration), 4, 8, 12 (+/- 30 minutes) and 24 (+/- 1 hour) hours post dose. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post ABT-199 administration.
    - IV hydration should be started with a target of approximately 2 L per day, or as clinically appropriate, for subjects who are hospitalized.
    - Hematology laboratory tests will be performed 24 hours post-dose.
    - The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital or receiving any additional doses of the study drug.
    - Chemistry and Hematology laboratory tests for all subjects treated in the outpatient setting must be collected within 72 hours prior to the first dose of ABT-199 of each dose escalation, and results must be reviewed by the investigator prior to each escalation. For subjects demonstrating any clinically significant laboratory abnormalities, additional prophylactic treatment should be administered prior to dosing (see Appendix B; Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]).

5.4 General Concomitant Medication and Supportive Care Guidelines

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.
Anti-emetics are permitted if clinically indicated. Standard supportive care medications are permitted. All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to

start and after start of study drug, including physical therapy and blood transfusions, should be recorded. The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants.
- No anticancer agents other than the study medication should be given to participants. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Growth factors (i.e. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) can be administered prophylactically, except to eligibility, and may be prescribed at the discretion of the treating physician for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria.
- Transfusions (red blood cells, platelets) can be administered to meet eligibility and for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria.
- Concurrent administration of ABT-199 and moderate or strong CYP3A4 inhibitors (such as clarithromycin, ketoconazole, itraconazole, and ritonavir) and inducers (such as rifampin and rifabutin) should be avoided. Alternatives should be sought if possible. During the ramp-up phase, moderate or strong CYP3A4 inhibitors and inducers are prohibited.
    - If subjects require use of moderate or strong CYP3A inhibitors after the ramp-up phase, use with caution and reduce the venetoclax dose by 50% for moderate inhibitors and at least 75% for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 2 to 3 days before increasing venetoclax dose back to maintenance/target dose.
    - If subject requires use of moderate or strong CYP3A inducers after the ramp-up phase and provided there is no alternative treatment available, the Principal Investigator should be consulted, and treatment should be administered with caution; patients should be closely monitored for potential lack of efficacy.

Examples of moderate and strong CYP3A inhibitors and inducers are provided in Table 5-1.

- If venetoclax is co-administered with warfarin, the international normalized ratio (INR) should be monitored closely.
- Grapefruit and grapefruit juice affect CYP450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No green tea or foods/supplements containing green tea or extract.
- No chronic treatment with systemic steroids (at dosages equivalent to prednisone >20 mg/day) or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

Inhibitors of CYP3A4 are defined as follows. Examples of moderate and strong CYP3A inhibitors and inducers are provided in Table 5-1.The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below:

- A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. Strong inhibitors are capitalized in the list below.

- A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.
- A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

Table 5-1 Moderate and Strong Inhibitors and Inducers of CYP3A4/5

Inhibitors of CYP3A4/5	**Inducers of CYP3A4/5**
Strong inhibitors:	
Boceprevir	**Strong CYP3A inducers:**
Clarithromycin	Avasimibe
Cobicistat	Carbamazepine
Conivaptan	Enzalutamine
Danoprevir/ritonavir	Mitotane
Elvitegravir/ritonavir	Phenytoin
Idelalisib	Rifampin
Indinavir	St. John's wort
Itraconazole	
Ketoconazole	**Moderate CYP3A inducers:**
Mibefradil	Bosentan
Lopinavir/ritonavir	Efavirenz
Nefazodone	Etravirine
Nelfinavir	Modafinil
Ritonavir	Nafcillin
Paritaprevir/ritonavir combinations	
Posaconazle	
Squinavir	
Telaprevir	
Telithromycin	
Tipranavir/ritonavir	
Voriconazole	
Moderate inhibitors:	
Amprenavir	
Aprepitant	
Atazanavir	
Cimetidine	
Ciprofloxacin	
Clotrimazole	
Crizotinib	
Cyclosporine	
Darunavir/ritonavir	
Diltiazem	
Erythromycin	
Fluconazole	
Fosamprenavir	
Imatinib	

Isavuconazole Tofisopam Verapamil	

Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruits.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of one of the above, treatment may continue for total drug study duration of 26 cycles (2 years), 25 cycles at the target dose, or until one of the following criteria applies:

- Confirmed disease progression or development of new signs or symptoms of disease;
- Development of symptomatic hyperviscosity
- Lack of response to signs or symptoms that prompted therapy after 12 weeks of therapy (defined as non-responder);
- Commencement of new anti-neoplastic therapy (including radiation therapy) for WM or other malignancy including myelodysplasia or WM disease transformation;
- Intercurrent illness or hold of study drug for any other reason for >28 days;
- Unacceptable adverse event(s);
- In the study team's opinion, participant has demonstrated an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements;
- Participant decides to withdraw from the study;
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

Special mentions:

For participants meeting criteria for disease progression (based on consensus panel criteria for IgM response) but are deemed by the investigator to be clinically benefiting from ABT-199, these individuals will be permitted to continue on protocol therapy at the principal investigator's discretion. Documentation describing the rationale for continuing benefit shall be entered into the medical record. Clinical benefit will be determined by considering clinical data, such as overall participant performance and disposition, complete blood counts, and when necessary, results from bone marrow biopsies and/or CT scans. In such instances, any new nadir that may result with continued therapy will be used as the study nadir point for this patient. Patients must be on $\geq$2 consecutive weeks of therapy for determination of a reliable IgM reading for response assessment purposes.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant. For Decentralized Subject Registrations, the Coordinating Center study staff updates the relevant Off Treatment/Off Study information in OnCore.
In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, *Jorge J. Castillo* at *617-632-6045*.

5.6 Duration of Follow Up

Participants will be followed up for the duration of the study treatment and for 2 years after completion of the study, or next therapy, whichever comes first. Patients will be seen every 6 months in the follow-up phase. Participants removed from study for unacceptable adverse events will be followed for 2 years or until next therapy.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study treatment, but will continue to be followed-up, when any of the criteria listed in Section 5.5 applies for up to 2 years or until the participant is lost to follow-up, withdraws consent, starts next therapy, or death. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant. In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator, Jorge J. Castillo, MD, at 617-632-6045.

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.). All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted. If administration of ABT-199 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 6-1.

If dose reductions of ABT-199 are needed during the lead-in period, dose escalation should continue on a weekly basis to reach the targeted dose of 800 mg PO daily (e.g. if a participant cannot tolerate the 400mg dose escalation, they should be reduced back to 200mg for 1 week, and then re-challenged at 400mg the following week, etc). In this case, the lead-in period could last for >4 weeks. Once at goal dose of 800 mg PO daily, dose reductions are permitted down to 100 mg PO daily before a patient is taken off study. However, patients will remain on study to assess for progression. If a participant requires a dose delay of 28 days or more, then the participant must be discontinued from the study.

Table 6-1. ABT-199 Dose Modification Guidelines Lead-in Phase Cohort 1

Lead-in Phase ABT-199 dosing	ABT-199 Dose level 1	Dose level -1	Dose level -2	Dose level -3	Dose Level -4
Week 1 starting dose	200mg	100mg	-	-	-
Week 2 1st dose escalation	400mg	200mg	100mg	-	-
Week 3+ Escalation to target dose and all cycles therafter	800mg	600mg	400mg	200mg	100mg

Table 6-2 ABT-199 Dose Modification Guidelines Lead-in Phase Cohort 2

Post Lead-in Phase ABT-199 dosing	ABT-199 Dose level 1	Dose level -1	Dose level -2	Dose level -3	Dose Level -4
Week 1 starting dose	400mg	200mg	100mg	-	-
Week 2+ Escalation to target dose and all cycles therafter	800mg	600mg	400mg	200mg	100mg

Dosing will be held for any of the following conditions:

- Grade 4 ANC (<500/μL) for >7 days (neutrophil growth factors are permitted).
- Grade 4 Platelets (<25,000/μL) or in subjects with baseline thrombocytopenia, decrease of > 75% from baseline or <20,000/ μL, whichever is higher. Hold until grade 3 unless active bleeding.
- Grade 3 or 4 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy).
- Any other related grade 4 toxicities and any unmanageable non-hematologic Grade 3 toxicities.

Drug Modification/Discontinuation Actions for ABT-199-related events

- 1st Hold: ABT-199 until recovery from criteria to hold; may restart at original dose level.
- 2nd Hold: ABT-199 until recovery from criteria to hold; restart at -1 dose level.
- 3rd Hold: ABT-199 until recovery from criteria to hold; restart at -2 dose level (if applicable, see tables 6-1 and 6-2)
- 4th Hold: ABT-199 until recovery from criteria to hold; restart at -3 dose level (if applicable, see tables 6-1 and 6-2)
- 5th Hold: ABT-199 until recovery from criteria to hold; restart at -4 dose level (if applicable, see tables 6-1 and 6-2
- 6th Hold: Discontinue ABT-199

If a participant has a drug hold, the schedule of assessments will not change. If participants do not meet treatment criteria on Day 1 of the cycle, the cycle will not be delayed.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for ABT199

Most subjects (89.6%) reported at least 1 adverse event. The most common adverse events were nausea (31.3%), diarrhea (29.2%), neutropenia (25.5%), fatigue (22.9%), and upper respiratory tract infection (22.4%). A summary of the treatment-emergent adverse events reported in > 10%

subjects treated with ABT-199 monotherapy, and relationship to study drug, is presented in Table 7-1.

Table 7-1. Treatment-Emergent Adverse Events in >10% of Subjects Treated with ABT-199 Monotherapy and Relationship to Study Drug

System Organ Class MedDRA 16.1 Preferred Term	ABT-199 Monotherapy Total (N = 192)	
	n (%)	Related[a] n (%)
Any adverse event	172 (89.6)	127 (66.1)
Blood and lymphatic system disorders		
Anaemia	30 (15.6)	16 (8.3)
Neutropenia	49 (25.5)	46 (24.0)
Thrombocytopenia	20 (10.4)	16 (8.3)
Gastrointestinal disorders		
Constipation	24 (12.5)	5 (2.6)
Diarrhoea	56 (29.2)	34 (17.7)
Nausea	60 (31.3)	40 (20.8)
Vomiting	23 (12.0)	11 (5.7)
General disorders and administration site conditions		
Fatigue	44 (22.9)	22 (11.5)
Pyrexia	30 (15.6)	8 (4.2)
Infections and infestations		
Upper respiratory tract infection	43 (22.4)	0
Nervous system disorders		
Headache	22 (11.5)	8 (4.2)
Respiratory, thoracic, and mediastinal disorders		
Cough	30 (15.6)	0

a. Considered possibly or probably related to ABT-199 by the investigator.

Note: A subject who reported the same MedDRA preferred term more than once was counted only once for that MedDRA term, once for each applicable system organ class, and once for overall.

A summary of adverse events NCI CTCAE grade 3 and above reported in more than 1% of the subjects treated with ABT-199 monotherapy, and relationship to study drug, is presented in Table 7-2. The most common adverse events grade 3 and above were neutropenia (21.9%) and anemia (12.0%).

Table 7-2. Treatment-Emergent Adverse Events NCI CTCAE Grade 3 and Above in > 1% of the Subjects Treated with ABT-199 Monotherapy and Relationship to Study Drug

System Organ Class MedDRA 16.1 Preferred Term	ABT-199 Monotherapy Total (N = 192)	
	n (%)	Related[a] n (%)
Any adverse event grade 3 or above	111 (57.8)	72 (37.5)
Blood and lymphatic system disorders		
Anaemia	23 (12.0)	10 (5.2)
Autoimmune thrombocytopenia	3 (1.6)	0
Febrile neutropenia	10 (5.2)	8 (4.2)
Leukopenia	6 (3.1)	5 (2.6)
Neutropenia	42 (21.9)	41 (21.4)
Thrombocytopenia	12 (6.3)	9 (4.7)
General disorders and administration site conditions		
Fatigue	3 (1.6)	0
Infections and infestations		
Lung infection	3 (1.6)	0
Pneumonia	3 (1.6)	1 (0.5)
Investigations		
Blood lactate dehydrogenase increased	3 (1.6)	3 (1.6)
Neutrophil count decreased	3 (1.6)	2 (1.0)
Metabolism and nutrition disorders		
Hyperglycaemia	8 (4.2)	1 (0.5)
Hypokalaemia	6 (3.1)	1 (0.5)
Hypophosphataemia	4 (2.1)	0
Tumor Lysis Syndrome	9 (4.7)	9 (4.7)
Musculoskeletal and connective tissue disorders		
Back pain	3 (1.6)	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Malignant neoplasm progression	5 (2.6)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	3 (1.6)	1 (0.5)

a. Considered possibly or probably related to ABT-199 by the investigator.

Note: A subject who reported the same MedDRA preferred term more than once was counted only once for that MedDRA term, once for each applicable system organ class, and once for overall.

A summary of serious adverse events reported in more than 1% of the subjects treated with ABT-199 monotherapy, and relationship to study drug, is presented in Table 7-3. The most common serious adverse event was febrile neutropenia (4.2%).

Table 7-3. Treatment-Emergent Serious Adverse Events Reported in > 1% of the Subjects Treated with ABT-199 Monotherapy and Relationship to Study Drug

System Organ Class MedDRA 16.1 Preferred Term	ABT-199 Monotherapy Total N = 192 N (%)	 Related[a] N (%)
Any serious adverse event	65 (33.9)	21 (10.9)
Blood and lymphatic system disorders		
Autoimmune thrombocytopenia	3 (1.6)	0
Febrile neutropenia	8 (4.2)	7 (3.6)
Infections and infestations		
Influenza	3 (1.6)	2 (1.0)
Pneumonia	3 (1.6)	1 (0.5)
Metabolism and nutrition disorders		
Tumor lysis syndrome	3 (1.6)	3 (1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Malignant neoplasm progression	4 (2.1)	0

a. Considered possibly or probably related to ABT-199 by the investigator.

Note: A subject who reported the same MedDRA preferred term more than once was counted only once for that MedDRA term, once for each applicable system organ class, and once for overall.

Ten of 192 (5.2%) subjects treated with ABT-199 monotherapy experienced adverse events that led to death. The most common adverse event that led to death was malignant neoplasm progression (4 subjects, 2.1%). All other adverse events leading to death included small intestinal obstruction, multi-organ failure, sudden death (in the setting of TLS), pneumonia viral, mental status changes, and respiratory failure (0.5% each). No other deaths were attributed to ABT-199.

Nineteen of 192 (9.9%) subjects treated with ABT-199 monotherapy experienced adverse events that led to study discontinuation. The most common event that led to study drug discontinuation was malignant neoplasm progression (in 3 subjects, 1.6%). All other adverse events leading to discontinuation were reported in 1 subject (0.5%) each.

Tumor Lysis Syndrome

TLS is considered an adverse event of special interest (AESI).

There is a potential for TLS in subjects affected by hematologic malignancies, especially in those with bulky disease, elevated pretreatment lactate dehydrogenase (LDH) levels, elevated leukocyte count, renal dysfunction, and dehydration. The risk of TLS in patients with WM is, however, extremely rare. In fact, no cases of TLS have been described in WM patients in the

literature (PubMed search performed on 02/10/2015 without date or language restriction using the keywords: “waldenstrom*” AND “tumor lysis”), and we have not observed the occurrence TLS in our database, which includes approximately 1,500 patients with WM. For these reasons, we do not believe the risk stratification criteria for TLS used for CLL, NHL and MM are applicable in WM patients. To err on the side of safety, we will take TLS precautionary measures in all patients enrolled in the present study.

Based on nonclinical and clinical data available with ABT-199 administration, the identified and potential risks, besides TLS are nausea, diarrhea, hematological effects (including lymphopenia, neutropenia/febrile neutropenia, thrombocytopenia, and anemia), serious and/or opportunistic infections, and decreased spermatogenesis. In addition, as ABT-199 is being evaluated in subjects with relapsed/refractory disease and has potential immunomodulatory properties, the risks of Richter's Syndrome and secondary malignancies are closely monitored.

Hematological Effects

All hematological adverse events were identified via review of events reported in the Blood and Lymphatic Disorders System Organ Class (SOC). In particular, events of neutropenia/febrile neutropenia, anemia/hemoglobin decreased, and thrombocytopenia are reviewed and summarized below. Lymphopenia and opportunistic infections are discussed together.

Neutropenia/Febrile Neutropenia

Neutropenia and febrile neutropenia are potential risks of dosing with ABT-199 based on suspected Bcl-2 mechanism-based toxicity.

One of 192 subjects (0.5%) treated with ABT-199 monotherapy experienced a serious adverse event of neutropenia (considered related to ABT-199); no serious adverse events were reported in the combination therapy studies. None of the events of neutropenia were considered serious or resulted in deaths or discontinuations.

In ABT-199 monotherapy studies, 8 of 192 subjects (4.2%) experienced serious adverse events of febrile neutropenia; these events were considered related to ABT-199 treatment by the investigators in 7 subjects (3.6%). One monotherapy subject (0.5%) discontinued the study due to an adverse event of febrile neutropenia; there were no deaths due to febrile neutropenia. In the combination Study M13-365, 1 of 38 subjects (2.6%) experienced a serious adverse event of febrile neutropenia; this event was not considered related to ABT-199. Additionally, in the combination Study M12-630, 3 of 22 subjects (13.6%) experienced serious adverse events of febrile neutropenia; 2 of these (9.1%) were considered related to ABT-199 treatment. There were no deaths or discontinuations due to febrile neutropenia in any combination therapy studies.

The events of neutropenia/febrile neutropenia were observed across all ABT-199 oncology studies; however, data are confounded by underlying advanced hematological malignancies and multiple prior therapies in these subject populations. Furthermore, the higher percentage of these events in combination studies is confounded by the coadministration with chemotherapeutic agents bendamustine and rituximab (Study M12-630) and rituximab (Study M13-365), both of

which are known to be associated with neutropenia/febrile neutropenia.

Based on clinical observations with the 1st generation Bcl-2 inhibitor, navitoclax and in vitro colony-forming assays to assess Bcl-2-selective inhibitor effects on granulocyte precursors, it is possible that subjects treated with ABT-199 might experience neutropenia. Subjects with a history of neutropenia, who have received multiple prior therapies and/or have significant bone marrow involvement, may be at particular high risk. If determined to be clinically indicated by the treating physician in compliance with ASCO guidelines, G-CSF may be administered during dosing of ABT-199. The use of G-CSF support is strongly recommended for subjects with Grade 4 neutropenia (ANC <500/μL). If the subject presents with febrile neutropenia or Grade 4 neutropenia for more than one week despite the use of optimal G-CSF support, ABT-199 dosing should be interrupted until ANC recovery to >500/μL. ABT-199 may then be re-initiated at a lower dose as defined in Table 6.1. Subjects not responding to G-CSF despite ABT-199 interruption should undergo further evaluation to determine the etiology of the neutropenia.

Anemia

Only 1 of 192 subjects (0.5%) in the monotherapy studies experienced a serious adverse event of anemia; the event was considered to have a reasonable possibility of being related to ABT-199. Although the percentage of all adverse events of anemia was higher in combination studies when compared to monotherapy, the data are confounded by administration of chemotherapeutic agents. There were no serious adverse events of anemia in any of the combination therapy studies. None of the events resulted in deaths or discontinuations.

Thrombocytopenia

Thrombocytopenia is a mechanism-based toxicity of the first-generation Bcl-2/Bcl-XL dual inhibitor navitoclax (ABT-263). As a second-generation, Bcl-2-selective inhibitor, ABT-199 is not expected to exhibit this type of thrombocytopenia; nevertheless, adverse events of thrombocytopenia remain of interest as data are collected.

In ABT-199 monotherapy studies, only 1 of 192 subjects (0.5%) experienced a serious adverse event of thrombocytopenia; this event was considered possibly related to ABT-199 (the subject was in the NHL arm of Study M12-175). One additional monotherapy subject (0.5%) discontinued the study due to a nonserious adverse event of thrombocytopenia, which was considered probably related to ABT-199. There were no deaths due to thrombocytopenia. In the combination therapy studies, there were no serious adverse events of thrombocytopenia, and no deaths or discontinuations due to thrombocytopenia.

Additionally, 4 subjects in monotherapy studies (2.1%) reported autoimmune thrombocytopenia; 3 of which (1.6%) were both grade 4 and serious. All events occurred in the CLL arm of Study M12-175.

Lymphopenia and Opportunistic Infections

Lymphopenia is an expected pharmacologic effect of selective Bcl-2 inhibition by ABT-199, and

is one aspect of the therapeutic mechanism of action in the treatment of subjects with lymphoid malignancies. No subjects treated with ABT-199 as monotherapy or in combination with chemotherapy experienced a serious adverse event of lymphopenia. None of the events of lymphopenia resulted in deaths or discontinuations. Due to potential risk of opportunistic infections in subjects with lymphopenia, adverse events potentially related to opportunistic infections were identified using the Opportunistic Infections Product-Specific (Bcl-2 specific) Company MedDRA query (PMQ). In monotherapy studies, adverse events in 6 subjects (3.1%) were identified on the basis of this PMQ. These included 1 subject with an adverse event of nocardiosis (0.5%) and 5 subjects (2.6%) with events of oral candidiasis.

There is a potential for clinically significant lymphopenia in this study. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion, including appropriate prophylaxis for viral, fungal, bacterial or Pneumocystis infections. Potential for drug-drug interactions should be considered. Most anti-fungals are excluded and other commonly used agents may be cautionary or prohibited due to drug-drug interactions. Please refer to Table 1, Table 2 and Appendix B for a description of excluded and cautionary medications.

Serious Infections

Adverse events potentially related to serious infections were identified using the Infections and Infestations SOC.

A total of 22 of 192 subjects (11.5%) treated with ABT-199 monotherapy reported serious adverse events in the Infections and Infestations SOC. The most common serious adverse events for monotherapy were influenza and pneumonia (in 3 subjects, 1.6% each.) Of these, influenza was considered to have a reasonable possibility of being related to ABT-199 in 2 subjects (1.0%). One serious adverse event of pneumonia viral (0.5%) resulted in discontinuation of ABT-199 and subject death; this event occurred in the CLL arm of Study M12-175 at 400 mg ABT-199, and was considered not related to ABT-199 by the investigator.

Additionally, in the combination therapy Study M13-365, five of 38 subjects (13.2%) experienced serious adverse events (bronchitis bacterial, influenza, lung infection, pneumonia haemophilus, and rotavirus infection, in 1 subject each). Bronchitis bacterial, pneumonia haemophilus, and rotavirus infection were considered to have a reasonable possibility of being related to ABT-199. And in the combination therapy Study M12-630, 1 serious adverse event of urinary tract infection was reported, it was considered to have no reasonable possibility of being related to ABT-199. None of the adverse events in combination therapy studies resulted in discontinuation or death.

The types of infectious events observed were generally consistent with those anticipated in the population of heavily pretreated CLL/NHL subjects.

Cardiac Function

As a result of findings of mild reductions in myocardial contractility and cardiac output (but not blood pressure, heart rate, or ECG) observed following ABT-199 administration in the

anesthetized cardiovascular dog model at concentrations of ≥ 16 μg/mL (concentrations greater than the concentration of ABT-199 in humans [3.39 μg/mL at the 900 mg dose]).

Pre- and post-dose left ventricular ejection fraction (LVEF) assessments (multi-gated acquisition scan/echocardiogram) were collected per protocol in monotherapy Study M12-175. As of 03 February 2013, the mean baseline LVEF among 76 subjects for whom data were available is 64.25 mmHg (SD: 6.72 mmHg; range: 43.00 to 80.00 mmHg). Pre- and post-dose ABT-199 LVEF assessment is available for 14 subjects (all from Study M12-175). Of these 14 subjects, no subject had a decrease in LVEF of more than 10%. Additionally, there were no subjects with LVEF less than 40 mmHg (grade 3 post-dose).

Medical review of all events retrieved using the Cardiac Failure (narrow) SMQ identified no treatment-emergent serious or non-serious events of cardiac failure/left ventricular function decrease that were related to ABT-199 or resulted in discontinuation or death. Events of edema peripheral were reported at a frequency of 8% or lower in monotherapy studies and combination Studies M13-365 and M12-630. One event each (2.6%) of left ventricular dysfunction and pulmonary edema was identified in Study M13-365; both events were considered to have no reasonable possibility of being related to ABT -199 by the investigator and were confounded by relevant past medical history.

Thus, based on data to date, the Sponsor believes that there is no risk of decreased cardiac function/decrease in LVEF following ABT-199 administration.

Richter's Syndrome (RS) due to disease progression

The reported incidence of RS (the clinical pathologic transformation to an aggressive lymphoma) in the published literature ranges from approximately 2% to 3% to as high as 16%, depending on the characteristics of the population studied. The evolution to RS typically occurs via acquisition of new genetic alterations in the original clone or other mechanisms appearing to play a role in the minority of cases.

Disease progression due to RS was reported for a total of 18 of 160 subjects (11.3%) in the ABT-199 oncology clinical program. (This included 14 of 95 subjects in Study M12-175, 3 of 38 in Study M13-365, 1 of 17 in Study M13-982, and zero subjects in Genentech/Roche Studies GP28331 [N = 8] and GO28440 [N = 2]). Sixteen of 18 subjects (88.9%) had prior exposure to fludarabine. The median number of prior treatment regimens was 4 (range: 1 to 9). The majority of subjects (11 of 18, 61.1%) were diagnosed with CLL more than 5 years before study enrollment, with 7 (38.9%) being diagnosed more than 10 years before study enrollment. At the time of the RS diagnosis, 9 of 18 subjects (50.0%) were on study for less than 6 months, and most subjects (14 of 18, 77.8%) were on study for less than a year. Nine of 16 subjects (56.3%) with RS who were analyzed for 17p del status were positive for 17p del; this subject population was also heavily pretreated. The diagnoses were 17 subjects transformed to DLBCL, and 1 subject transformed to classic Hodgkin's Lymphoma.

The role of ABT-199 treatment in these cases is unclear. The frequency of RS cases observed to date in the ABT-199 oncology clinical program in subjects with CLL (11.3%) is within the range

of reported incidence for subjects with relapsed CLL previously treated with multiple prior therapies. Ongoing monitoring of subjects for the signs and symptoms of RS was implemented in ABT-199 clinical trials in the previous reporting period, including recommendations for performing a diagnostic biopsy to obtain pathology and examination for EBV and genetic markers, if possible.

Treatment-Emergent Malignancies

The risk of a secondary malignancy is increased in subjects with WM, particularly those who have undergone prior chemotherapy treatments. Additionally, due to the immunomodulatory mechanism of action of ABT-199, the risk of secondary malignancy cannot be ruled out.

A total of 5 treatment-emergent secondary malignancies were identified following medical review of events retrieved using the SOC of neoplasms benign, malignant, and unspecified of the Malignancies SMQ: bladder transitional cell carcinoma recurrent, lung adenocarcinoma, esophageal adenocarcinoma, prostate cancer, squamous cell carcinoma, and squamous cell carcinoma of the lung in 1 subject (0.5%) each. None of these events in monotherapy and combination therapy studies were considered to have a reasonable possibility of being related to ABT-199.

These events are consistent with that expected in an elderly population with relapsed hematological malignancies and a history of multiple prior therapies.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, all grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.4 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
Investigations	Neutrophil count decreased	4	No	Related	If hospitalization required, must be reported to DFCI IRB and PI

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Expedited Reporting to Abbvie Drug Safety Department

Adverse Events; **Pregnancy.** In addition to compliance with all FDA reporting requirements pursuant to 21 C.F.R. § 312, the Principal Investigator shall:

a. report all serious adverse events experienced by a study subject receiving an AbbVie product within 24 hours of learning of the event regardless of the relationship of the event to the AbbVie product. Principal Investigator shall make available to AbbVie promptly such records as may be necessary and pertinent to investigate any such event, if specifically requested by AbbVie; and in addition; report all non-serious adverse events of tumor lysis syndrome for studies involving ABT-199.
    i. Serious AE (SAE) means any untoward medical occurrence that meets one of the following criteria:
        i. Results in death
        ii. Is life-threatening
        iii. Requires inpatient hospitalization for >24 hours or prolongation of hospitalization
        iv. Is a congenital anomaly
        v. Results in persistent or significant disability/incapacity
        vi. Other serious (Important Medical Events) Events that do not fit the other outcomes but may require medical or surgical intervention to prevent one of the other outcomes.
b. copy AbbVie on the submission to the FDA of events meeting the definition of IND safety reports at the time of submission to the Agency; and

c. notify AbbVie upon any subject receiving an AbbVie Product whose pregnancy has resulted in a negative outcome or untoward event during the course of pregnancy or upon delivery.

AbbVie's contact for reporting serious adverse drug experiences, pregnancy experiences, non-serious adverse events of tumor lysis syndrome, and communication of FDA submissions of IND safety reports shall be *PPDINDPharmacovigilance@abbvie.com*

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

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

8.1 ABT-199

8.1.1 Description

ABT-199 has the molecular formula C45H50ClN7O7S and a molecular weight of 868.44. ABT-199 is a light yellow to dark yellow powder, and is freely soluble in vinylpyrrolidone dimer; soluble in polyethylene glycol (PEG) 400; very slightly soluble in 1% (w/v) Cremophor RH40, and is practically insoluble in water. There are no optical isomers.

8.1.2 Form

ABT-199 is provided as a yellow film-coated tablet in 50 and 100mg strength. 100mg tablets will be supplied for this study in 30 or 120 count bottles which must not be opened and re-packaged. It will be packaged in high density polyethylene (HDPE) plastic bottles to accommodate the study design. Each bottle will be labeled per regulatory requirements. Labels must remain affixed to the bottle.

8.1.3 Storage and Stability

The ABT-199 tablets must be stored at 15° to 25°C (59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label.

8.1.4 Availability

ABT-199 is provided to by Abbvie. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

8.1.5 **Administration**

ABT-199 should be self-administered daily by the participant and should be taken at approximately 30 minutes after breakfast or the first meal of the day, at approximately the same time each day. ABT-199 should be administered with 8 ounces (approximately 240 mL) of water (avoid GRAPEFRUIT JUICE due to CYP3A4 inhibition). The tablets should be swallowed intact. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the participant should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Dietary habits around the time of ABT-199 intake should be as consistent as possible throughout the study. If the pills are vomited this should be noted on the diary, but a replacement dose should not be taken that day. A study diary will be used to aid with study drug administration compliance.

Except for cycle 1 which may be longer, one cycle of ABT-199 is once daily, oral administration for 4 weeks ± 1 week. At each study visit, enough ABT-199 will be dispensed until the next cycle. For cycle 1, additional drug may be dispensed mid-cycle if necessary. For visits occurring monthly (every 4 weeks ± 1 week), one cycle of pills (5 weeks of ABT-199 therapy) will be dispensed. For visits occurring every 12 weeks ± 2 weeks), three cycles of pills (14 weeks) will be dispensed.

8.1.6 **Ordering**

ABT-199 is an investigational agent and will be supplied free-of-charge from AbbVie and Genentech/Roche.

The contact for ordering is:
iisoncologysupport@abbvie.com

8.1.7 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.8 **Destruction and Return**

Unused ABT-199 tablets will be returned by the participant, collected and counted at each study visit, and will be returned to pharmacy for destruction. Unused supplies of ABT-199 should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1 Laboratory Correlative Studies

Assessment of MYD88 L265P and CXCR4 WHIM genotyping.

An allele-specific polymerase-chain-reaction (PCR) assay will be used to detect $MYD88^{L265P}$ mutations. $CXCR4^{WHIM}$ mutation status will be determined by means of Sanger sequencing, and allele-specific PCR will be used to detect $CXCR4^{S338X}$ C→G and C→A mutations in CD19-selected bone marrow cells (Xu et al, 2013; Hunter et al,2014; Treon et al, 2014). For PCR assays two large lavender tops of bone marrow aspirate will be collected at the time of the screening bone marrow biopsy and each subsequent protocol mandated bone marrow biopsy.

10. STUDY CALENDAR

STUDY CALENDAR

	Screening * ≤ 30 days from study entry	**Treatment Phase[7]**		**Off Treatment Assessment** Within 4 weeks of completion of or removal from study ± 2 weeks	**Follow-Up Phase** Post Treatment; Every 24 weeks ± 2 weeks for 2 years or until next therapy
		Cycles 1*(4 weeks +2 days), 2 (4 weeks +/- 1 week)	Cycles 3, 6, 9, etc. until study completion (12 weeks ± 2 week)		
Physical exams[1], vital signs (Temp, HR, RR, BP), weight, height	X	X	X	X	X
ECOG performance status (see Appendix A)	X	X	X	X	X
CT of the chest & abdomen / pelvis[2]	X		X[2]	X[2]	X (if applicable)
Bone marrow biopsy and aspiration[3]	X		X[3]	X	X (if applicable)
Serum immuno-electropheresis	X	X	X	X	X
IgM		X***			
Complete Blood Count plus differential[1,4]	X	X**	X	X	X
Coagulation profile: PT, PTT, PT-INR[5]	X				
Chemistry including: Electrolytes, Renal (BUN, Creatinine) and Hepatic function testing [ALT (SGPT), AST (SGOT), Alk phos, total Bilirubin], albumin, total protein	X	X**	X	X	X
Tumor lysis labs: Potassium, Creatinine, Bicarbonate, Calcium, Phosphorus, LDH, uric acid	X	X**			
Magnesium	X	X			
Beta-2 microglobulin, HIV, Von Willebrand	X				
Pregnancy Test[6]	X				
HBsAg, HBsAb, HBcAB	X				
HCV Ab	X				

Response Assessment		X	X	X	X
Review patient diary		X	X		
Adverse event monitoring (see section 6)		X	X	X	X

* Physical exam, vital signs, and weight do not need to be repeated if Cycle 1, Day 1 is within 14 days of Screening. Cycle 1, Day 1 labs, to be collected within 72 hours prior to first dose of ABT-199, do not need to re-confirm eligibility prior to administering first dose.

**TLS monitoring and management will depend on criteria in section 5.1 *Tumor Lysis Syndrome*. All Chemistry and TLS laboratories will be drawn on dose escalation days at 0 hour, 8 hours post dose, and 24 hours post dose until the target dose is reached. Hematology labs should be done at 0 hours and 24 hours post dose until the target dose is reached. At a minimum they will be drawn during. Cycle 1 on Days 1, 8, and 15 for the first six participants (cohort 1), and Cycle 1 Day 1 and 8 for all other participants (cohort 2).

*** IgM will be monitored weekly for the first 6 weeks of study treatment for all participants (i.e. Days 1,8, 15, 22, 29, and 36 +/- 2 days) to evaluate the potential for IgM flare.

[1]More frequent visits may be required at the discretion of the treating physician.

[2]**If CT scans of the chest, abdomen and pelvis have been collected and done within 90 days of C1D1 they will not be required at the screening visit.** Scans will be **repeated at cycles 6, 12, and EOT for participants with extramedullary disease at baseline <u>defined as adenopathy >1.5 cm in any axis, and splenomegaly >15 cm in the craniocaudal axis</u>.** Scans will also be repeated to confirm a complete response if the participant has no detectable monoclonal protein and had extramedullary disease at baseline and at the discretion of the investigator.

[3]**If a bone marrow biopsy and aspiration was done within 90 days of C1D1, it will not be repeated.** Bone marrow biopsy and aspiration are **required at cycles 6, 12, and EOT**. Bone marrow biopsy and aspiration may also be done at the investigator's discretion, and at any time to confirm a complete response if the participant has no detectable monoclonal protein. MYD88 and CXCR4 mutational status will be assessed at each bone marrow biopsy.

[4]For patients who demonstrate therapy-related hematoxicity, more frequent CBC evaluations are strongly recommended.

[5]Coagulation profile. Prothrombin time (PT) will be performed at screening and repeated as clinically indicated. PT will be reported as well as the international normalized ratio (INR) and PTT.

[6]For women of childbearing potential only: Serum pregnancy test is required at screening.

[7]Please refer to Section 6 for Dose Modifications

11. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be re-evaluated for response every 4 weeks ± 1 week for cycles 1, 2, and 3 and thereafter every 12 weeks ± 2 weeks for the remaining cycles for a total of 4 years, and within 4 weeks ± 2 weeks from when a participant is removed from trial or when treatment is completed. IgMs measured during Cycle 1 are only for evaluation of potential IgM flare and should not be used for response or nadir determination. Post-treatment, patients will continue to be followed-up every 12 weeks ± 2 weeks for 2 years. Participants will be assessed for efficacy by consensus panel criteria according to section 11.1.1 below adopted from the Third International Workshop on WM (Anderson et al, 2012).

11.1 Antitumor Effect – Hematologic Tumors

11.1.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

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

11.1.2 Response Criteria

Complete Response (CR): A complete response (CR) is defined as having resolution of WM related symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A complete response requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.

Very Good Partial Response (VGPR): is defined as $\geq$ 90% reduction in serum IgM levels, or normalization of serum IgM levels.

Partial Response (PR): Partial response (PR) is defined as achieving a $\geq$ 50% reduction in serum IgM levels.

Minor Response (MR): A minor response (MR) is defined 25-49% reduction in serum IgM levels.

Progressive Disease (PD): Progressive disease (PD) is defined as occurring when a greater than 25% increase in serum IgM level occurs with an absolute increase of at least 500 mg/dL from the lowest attained response value, or progression of clinically significant disease related

symptom(s). Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation. Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event. For participants on active therapy who are on a drug hold for > 7 days, serum IgM levels will be considered unevaluable for response assessment. Patient must be on study drug for >2 consecutive weeks to be considered eligible for serum IgM response assessment. An increase of 1 cm in any axis for adenopathy, or 2 cm in the craniocaudal axis of the spleen will be considered evidence of progression of extramedullary disease. Development of Bing Neel syndrome, or other extramedullary disease manifestations, as well as disease transformation will be considered as progressive events.

Stable Disease (SD): Stable disease is defined as having < 25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM.

Overall Response Rate (ORR): Includes patients who achieved MR, PR, VGPR and CR.

11.1.3 Confirmation of Response

Confirmation of response will be done by bone marrow biopsy at cycles 6, 12, 24, 36 and 48 and in the case of extramedullary disease by CT scans at cycles 6, 12, 24, 36 and 48.

11.1.4 Time-to-event definition

- Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression (including initiation of new therapy or death). Median, 2-year and 4-year landmark PFS analysis will be determined.
- Overall survival (OS) is defined as the duration of time from start of treatment to time of death or last follow-up. Median, 2-year and 4-year landmark OS analysis will be determined.
- Time to Progression (TTP) for a given subject will be defined as the number of days from the date the subject started study drug to the date of the subject's tumor progression as defined in Section 11.1.1. Time to tumor progression may be collected up to 12 weeks following the last available tumor evaluation. All events of tumor progression will be included, regardless of whether the event occurred while the subject was still taking study drug, or after the subject discontinued study drug. If a subject has not progressed, then the data will be censored at the last study visit at which a tumor assessment was performed.
- The duration of response (DOR) for a given subject will be defined as the number of days from the day the criteria are met for ORR to the date that PD is objectively documented. The reference for PD will be the smallest IgM measurements recorded since the treatment started. If a subject is still responding then the subject's data will be censored at the last study visit at which a tumor assessment was performed.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix C.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Collaborative Agreements Language

N/a

13. STATISTICAL CONSIDERATIONS

This is single arm, open label, Phase II study designed to evaluate the safety and efficacy of ABT-199 in previously treated, relapsed/refractory WM patients. Therapy will be administered daily to patients with WM, and patients will receive treatment until progression or unacceptable toxicity for 2 years after completion of the lead-in phase.

Study Design/Endpoints

The primary endpoint of the current study is:

- To assess the overall response rate (ORR) of ABT-199 in symptomatic WM patients with relapsed/refractory disease.

The final analysis for the primary endpoint, overall response rate (minor response or better), will be conducted at 6 months after the enrollment of the last subject, and will be based on the evaluable population. The evaluable population is defined as all enrolled subjects who have received at least 1 dose of study drug and who have at least 1 adequate post-baseline disease assessment. Adequate disease assessment is defined as having sufficient evidence to correctly indicate that progression has or has not occurred. Subjects who died due to progression are also considered to have had adequate assessment.

13.1 Study Design/Endpoints

The primary endpoint of this study is to assess the Overall Response Rate (MR or better). Major response rates (PR or better), and Very Good Partial Response/Complete Response (VGPR/CR) of ibrutinib in previously treated, symptomatic WM patients will also be evaluated. The analysis for the primary endpoint, Overall response rate (MR or better), will be based on the evaluable population. The evaluable population will be defined as all enrolled participants. The overall response rate and its exact 95% confidence intervals (CI) will be calculated and the null hypothesis will be rejected if the lower bound of the 95% confidence interval exceeds 40%. The analysis for major response (PR or better) will be similarly evaluated. In addition, the number and percent of subjects by best overall response (CR, VGPR, PR, MR, SD, or PD) will be summarized.

13.2 Sample Size, Accrual Rate and Study Duration

Following a Fleming's one step approach, and assuming a null (H0) ORR of 40% (based on

previous experience on single-agent efficacy in patients with WM), and an alternative (H1) ORR of 70%, a total of 30 evaluable patients need to be accrued to show the proposed difference with an alpha (type I error) of 0.04 and a power (1-beta or type II error) of 90%, based on a binomial model (STATA version 13.1). 3 participants were determined to be non-evaluable, so a total of 33 participants will be enrolled. Therefore, if less than 18 patients achieved at least a minor response, the null hypothesis cannot be rejected and further research with ABT-199 in patients with WM should not be pursued. On the other hand, if 18 or more patients achieve at least a minor response (18/30 patients ORR 60%, 95% CI 42-75%), the null hypothesis will be rejected and further research with ABT-199 in patients with WM would be warranted. The expected accrual rate is 2-4 participants per month, for a an expected accrual time of 9-12 months.

13.3 Stratification Factors

No stratification factors will be applied to any analysis.

13.4 Interim Monitoring Plan

Refer to section 13.6

13.5 Analysis of Primary Endpoints

Refer to section 13.6

13.6 Analysis of Secondary Endpoints

The secondary endpoints are:

- To assess the safety and tolerability of ABT-199 in symptomatic WM patients with relapsed/refractory disease.
- To evaluate the rate of CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) and progressive disease (PD)
- To evaluate the median, 2-year and 4-year PFS and OS, and median duration of response (DOR)
- To evaluate the toxicity profile of ABT-199 in patients with relapsed/refractory WM
- To determine the MYD88 L265P mutational status in response to ABT-199 in patients with relapsed/refractory WM
- To evaluate the association between depth of response and quantification of MYD88 L265P burden by PCR
- To evaluate the association between presence of CXCR4-WHIM-like mutations and response to ABT-199

DOR, PFS and OS analysis will be performed using the Kaplan-Meier methodology, and participants will be censored at the time of last relevant assessment if they have not demonstrated the event of interest by the end of the study. Analysis of TTP, DOR, PFS and OS analysis will be

conducted at the same cutoff as the overall response rate, and an update of these endpoints will be provided at the end of the study.

In recent studies, the MYD88 and CXCR4 mutational status are predictive of clinical status, response to therapy and survival outcomes (Cao 2013, Treon 2013, Treon 2014). Activating MYD88 as well as nonsense and frameshift WHIM-like CXCR4 somatic mutations are common in Waldenström macroglobulinemia. CXCR4 nonsense mutations are present in aggressive cases including hyperviscosity syndrome, and MYD88 status is a determinant of survival. The MYD88 L265P mutational analysis by allele-specific PCR and CXCR4 mutational analysis by Sanger sequencing will be performed by the Bing Center for Waldenström Macroglobulinemia in Boston, MA.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants who receive at least one dose of any test material during the study will be included in the safety analysis.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned a response category based on the response criteria in Section 11.1.1.

All participants who met the eligibility criteria and were enrolled in the trial will be included in the main analysis of the response rate. All conclusions will be based on all eligible participants.

14. PUBLICATION PLAN

Any formal presentation or publication of data from this trial may be published after review and comment by Abbvie, Inc. prior to any outside submission. Abbvie, Inc. must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Abbvie, Inc.'s responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Abbvie, Inc. and, in accord with the trial contract and shall not permit disclosure of Abbvie, Inc. confidential or proprietary information.

Abstracts will be submitted, and presented if accepted as poster or oral presentation, at the ASH Annual Meeting and at the EHA Annual Meeting on a yearly basis while the study is ongoing. The final manuscript will be compiled and submitted for publication in approximately 2 years of the end date of all data collection with an updated publication at 4-year landmark analysis.

REFERENCES

Bajwa N, Liao C, Nikolovska-Coleska Z. Inhibitors of the anti-apoptotic Bcl-2 proteins: a patent review. Expert Opin Ther Pat 2012; 22: 37-55.

Cao Y, Hunter ZR, Liu X, et al. The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents in the treatment of Waldenstrom's Macroglobulinemia. Leukemia 2014 [Epub ahead of print]

Castillo JJ, Olszewski AJ, Cronin AM, et al. Survival trends in Waldenström macroglobulienia: an analysis of the Surveillance, Epidemiology and End Results database. Blood 2014; 123(25): 3999-4000.

Davids MS, Seymour JF, Gerecitano JF, et al. Phase I study of ABT-199 (GDC-199) in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL): Responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses. J Clin Oncol (Meeting Abstracts) 2104; 32(15_s): 8522.

Fesik SW. Promoting apoptosis as a strategy for cancer drug discovery. Nat Rev Cancer 2005; 5(11): 876-85.

Gertz MA, Geyer SM, Badros A et al. Early results of a phase I trial of oblimersen sodium for relapsed or refractory Waldenstrom's macroglobulinemia. Clin Lymphoma 2005; 5: 282-284.

Hatjiharissi E, Mitsiades CS, Bryan CT et al. Comprehensive Molecular Characterization of Malignant and Microenvironmental Cells in Waldenstrom's Macroglobulinemia by Gene Expression Profiling. ASH Annual Meeting Abstracts 2007; 110: 3174-.

Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood 2014; 123(11): 1637-46.

Kyle RA, Treon SP, Alexanian R, et al. Prognostic markers and criteria to initiate therapy in Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol 2003; 30(2): 116-20.

Leleu X, Soumerai J, Roccaro A et al. Increased incidence of transformation and myelodysplasia/acute leukemia in patients with Waldenstrom macroglobulinemia treated with nucleoside analogs. J Clin Oncol 2009; 27: 250-255.

Ogmundsdottir HM, Einarsdottir HK, Steingrimsdottir H, Haraldsdottir V. Familial predisposition to monoclonal gammopathy of unknown significance, Waldenstrom's macroglobulinemia, and multiple myeloma. Clin Lymphoma Myeloma 2009; 9: 27-29.

Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenström's

Macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenström's Macroglobulinemia. Semin Oncol 2003; 30(2): 110-115.

Owen RG, Kyle RA, Stone MJ, et al. Response assessment in Waldenström macroglobulinaemia: update from the VIth International Workshop. Br J Haematol 2013; 160(2): 171-6.

Paulus A, Chitta K, Akhtar S et al. AT-101 downregulates BCL2 and MCL1 and potentiates the cytotoxic effects of lenalidomide and dexamethasone in preclinical models of multiple myeloma and Waldenstrom macroglobulinaemia. Br J Haematol 2014; 164: 352-365.

San Miguel JF, Vidriales MB, Ocio E et al. Immunophenotypic analysis of Waldenstrom's macroglobulinemia. Semin Oncol 2003; 30: 187-195.

Sekhar J, Sanfilippo K, Zhang Q, et al. Waldenström macroglobulinemia: a Surveillance, Epidemiology, and End Results database review from 1988 to 2005. Leuk Lymphoma 2012; 53(8): 1625-6.

Seymour JF, Davids MS, Pagel JM, et al. ABT-199 (GDC-199) in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL): High complete response rate and durable disease control. J Clin Oncol (Meeting Abstracts) 2014; 32(15_s): 7015.

Souers AJ, Leverson JD, Boghaert ER et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med 2013; 19: 202-208.

Swerdlow SH, Berger F, Pileri SA et al. Lymphoplasmacytic lymphoma. In Swerdlow SH, Campo E, Harris NL et al. (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC 2008; 194-195.

Treon SP. How I treat Waldenström macroglobulinemia. Blood. 2009;114(12):2375-85.

Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med 2012; 367(9): 826-33.

Treon SP, Tripsas CK, Yang G, et al. A prospective multicenter study of the Bruton's Tyrosine Kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenstrom's Macroglobulinemia. ASH Annual Meeting Abstracts 2013; 122(21): 251.

Treon SP, Cao Y, Xu L, et al. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom's macroglobulinemia. Blood 2014; 123(18): 2791-6.

Yang G, Zhou Y, Liu X, et al. A mutation in MYD88 (L265P) supports the survival of lymphoplasmacytic cells by activation of Bruton tyrosine kinase in Waldenstrom macroglobulinemia. Blood 2013; 122(7): 1222-32.

APPENDIX A PERFORMANCE STATUS CRITERIA

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

APPENDIX B: Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

Section 1: First Dose of ABT-199 or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional ABT-199 doses should be administered until resolution. Rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to the recommendations in the table below, for subjects receiving the first dose of ABT-199:

- For potassium increase ≥ 0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.

Abnormality	**Management recommendation**
Hyperkalemia (Including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal • (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor

	lysis. • At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. • Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hrs., if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate.

	• Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose based on local guidelines and/or institutional standards). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose based on local guidelines and/or institutional standards). • When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs. later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and • 4 hrs. later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis

	service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

Section 2: Ongoing Dosing of ABT-199

Management of electrolyte changes from last value at intervals > 24 hours after either the first dose or dose escalation (e.g., 48 or 72 hours) are as below.

Note: If the patient is hospitalized, no additional ABT-199 doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
- Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further ABT-199 dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see prior table).

APPENDIX C. DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperruricemia	Uric acid > 8.0 mg/dl (475.8µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dl (1.5mmol/liter) in adults or > 6.5 mg/dl (2.1 mmol/liter) in children	
Hyperkalemia	Potassium > 6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dl (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter) †	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, Carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia.
Acute kidney injury‡	Not Applicable	Increase in the serum creatinine level of 0.3 mg/dl (26.5 µmol/liter) (or a single value > 1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 ml/kg/hr for 6 hrs

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4- albumin in grams per deciliter).

‡ Acute kidney injury is definited as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguia lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injurt from Levin at al.

Note: In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

APPENDIX D MULTICENTER GUIDELINES

DFCI IRB Protocol #: 15-491

APPENDIX *D*

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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15. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

15.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

15.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (FDA). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Office of Data Quality/Clinical Trial Research Informatics Office: Groups within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

16. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

16.1 DF/HCC Sponsor

The DF/HCC Sponsor, **Jorge J. Castillo,** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials, as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

16.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions with OnCore
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

16.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.

- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

17. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

17.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

17.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening

protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

17.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

17.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

17.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

17.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

17.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ/OnCore case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

17.7 DF/HCC Multi-Center Protocol Registration Policy

17.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and faxed (617-632-6752) or e-mailed (kirsten_meid@dfci.harvard.edu) to the Coordinating Center

- Copy of serum protein electropheresis, CBC with diff, Chemistries, CT C/A/P, bone marrow biopsy
- Screening visit note
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Eligibility Checklist

The Eligibility Checklist should be filled out by a clinical study staff member and the "Screening Staff" section must be signed by them. Study staff at the Coordinating Center will review the eligibility documentation and sign as the "Enrollment Monitor."

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101B) and register the participant on the protocol in OnCore. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Time.

17.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

17.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

17.8 DF/HCC Protocol Case Number

At the time of registration, ODQ/OnCore requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

17.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

17.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

17.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

17.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

17.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section *7.*

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

17.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

17.10 Data Management

The DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC CTRIO provides a web based training for eCRF users.

17.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC CTRIO Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed on a monthly basis.

18. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section *8.1.6.*

Participating Institutions should order their own agent regardless of the supplier.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent so that any regulatory responsibilities can be met in a timely fashion.

19. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

19.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement on-site as well as virtual ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and

protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Additionally, regular and ongoing communication with Participating Institutions will be accomplished by holding all site teleconferences at quarterly until enrollment is completed and the last participant in has been on study for at least 6 months. After this there will be teleconferences every 6 months until all participants are off treatment. Additional teleconferences will take place as needed for significant events (i.e. change in accrual, event involving participant, etc.) The Lead Institution will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or

Remote Monitoring

Participating Institutions will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. Each participant's initial consent and eligibility will be reviewed within 30 days of enrollment. Study visits and corresponding CRFs will be reviewed every 6 months for protocol compliance, AEs, SAEs, study drug administration, dose modifications, and follow-up of action items. Pharmacy records will be remotely reviewed every 6 months.

On-Site Monitoring

Participating Institutions will have annual on-site visits to for a Pharmacy site review, Regulatory binder review, and to meet with the site PI (if available).

Closeout Monitoring

Closeout monitoring will be done remotely at the end of the study.

19.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

19.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. Due to the small patient population, the accrual minimum requirement is at least 1 patient every two years.

20. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

20.1 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

20.2 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

20.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

20.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

20.5 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.