ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER
AFT – 15

A Phase I Study of Ibrutinib (PCI-32765) in Combination with Revlimid/Dexamethasone (Rd) in Relapsed/Refractory Multiple Myeloma

Protocol Version:3.0
Protocol Version Date: January 22, 2024

Investigational Product: Ibrutinib (PC-32765)
IND Sponsor: Alliance Foundation Trials, LLC
IND#: 140017
Investigational Product Supplier: Pharmacyclics LLC

ClinicalTrials.gov Identifier: NCT03702725

Protocol Contacts

<table>
<tr><td colspan="2">Sponsor Principal Investigator
Evanthia Galanis, MD Alliance
Foundation Trials, LLC
221 Longwood Avenue Suite 122
Brigham and Women's Hospital
Boston, MA 02215
Ph: [redacted]
Email:
[redacted]</td></tr>
<tr><td>Study Chair
Jacob P. Laubach, MD
Dana Farber Cancer Institute
450 Brookline Avenue
Mayer 222
Boston, MA 02215
Ph: [redacted]
Fax: [redacted]
Email: [redacted]</td><td>Study Chair
Yvonne A. Efebera, MD MPH
Division of Hematology and Blood and Marrow Transplant
OhioHealth
500 Thomas Lane
Columbus, OH 43014
Ph: [redacted]
Fax: [redacted]
Email: [redacted]</td></tr>
<tr><td>Primary Statistician
Vera J. Suman, PhD
Mayo Clinic
200 First St. SW
Rochester, MN 55901
Ph: [redacted]
Fax: [redacted]
Email: [redacted]</td><td>Correlative Science Co-chair:
Flavia Pichiorri, MS, PhD
Judy and Bernard Briskin Center for Multiple Myeloma Research
Division of Hematologic Malignancies and Stem Cell Transplantation Institute
City of Hope
1500 E. Duarte, CA 91010
Ph: [redacted]
Email: [redacted]</td></tr>
<tr><td>Executive Officer:
Shira Dinner, MD
Robert H. Lurie Medical Research Center
Northwestern University
303 E. Superior Chicago, IL 60611
Ph: [redacted]
Email: [redacted]</td><td>Project Manager:
Joseph Gannon
Project Manager
Alliance Foundation Trials, LLC
221 Longwood Avenue Room 108
Boston, MA 02115
Ph: [redacted]
Fax: [redacted]
Email: [redacted]</td></tr>
</table>

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Study Resources

The following study resource sites are accessible via the AFT website: [redacted] **Adverse Event Reporting via Medidata Rave® iMedidata Portal** **Medidata Rave® Balance – Randomization System Site Zone** For Site Zone Help: [redacted]
BiOMS AFT Resource Site [redacted]

Protocol-related questions may be directed as follows:

Questions	Contact
Questions regarding patient eligibility, treatment, dose modifications, protocol, IRB, model consent revisions, site regulatory documents, biospecimen collection, requirements, and processing, etc.	**AFT Clinical Research Associates** Email: [redacted]
Questions related to AE/SAE reporting	**Novella Clinical:** Safety Management Ph: US Toll Free: [redacted] Email: [redacted]

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Synopsis and Study Schema

Study Title	**A Phase I Study of Ibrutinib (PCI-32765) in Combination with Revlimid/dexamethasone (Rd) in Relapsed/Refractory Multiple Myeloma**
Study Number	AFT-15
Study Type/Phase	Phase Ib
Clinical Indication	Relapsed/Refractory Multiple Myeloma
ClinicalTrials.gov Identifier	NCT03702725
IND Number	140017
Number of Study Patients	19-25 (Dose escalation:9-18; Dose expansion: 4-10)
Estimated Duration of Trial	Approximately 42 to 48 months to enroll *Patients are treated until disease progression
Rationale	In the last decade, significant progress has been made in the treatment of Multiple Myeloma (MM), primarily due to the introduction of proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs). However, nearly all patients ultimately relapse and require further therapy, making the development of new compounds for MM therapy an important priority. Preclinical studies suggest synergism between lenalidomide and ibrutinib in MM. The anti-myeloma effects of lenalidomide have been previously described and include caspase-8-dependent apoptosis of MM cells, inhibition of angiogenesis, and activation of NK and T effector cells. Both ibrutinib and lenalidomide downregulate IRF4, a master transcriptional factor that mediates myeloma cell survival, and both exert effects on the BM microenvironment with overlapping yet distinct targets that influence MM cell growth and survival. The combination of lenalidomide and ibrutinib is thus an attractive therapeutic strategy not only as a potent anti-MM regimen but also in terms of positively impacting bone disease.

Primary Objective	1. To determine the maximum tolerated dose (MTD) in phase I and recommended dose in extension cohort of ibrutinib in combination with lenalidomide and dexamethasone 2. To examine the safety profile of ibrutinib in combination with lenalidomide and dexamethasone
Secondary Objectives	To determine the following: 1. Progression-free survival (PFS): Time from registration to disease progression or death due to any cause. 2. Overall survival (OS): Time from registration to death due to any cause. 3. Overall Response Rate: Time from start of treatment to objective response 4. Duration of response: Time from documented response to disease progression among those patients whose disease meets the IMWG criteria for disease response
Correlative Science Objectives	To perform select immunologic studies with this combination therapy.
Study Design	<u>Part 1: Dose Escalation</u> Patients in the dose escalation phase will receive oral treatment with: Ibrutinib: Days 1-28 of every 28-day cycle Lenalidomide: Days 1-21 of every 28-day cycle Dexamethasone: 40 mg for patients <75 at the time of registration 20 mg for patients ≥75 at registration on Days 1, 8,15 and 22 of every Cycle. One cycle is 28 days. Starting doses of ibrutinib and lenalidomide will be assigned at the time of registration. A minimum of 2 or a maximum of 6 patients will be accrued to a given dose level. Doses will not be escalated in any individual patient. If none of the first 3 patients treated at a given dose level develops a DLT during the first cycle of treatment, enrollment to the dose level will be closed and enrollment will reopen at next higher dose level. If there are no other higher dose levels to be tested, three additional patients will be enrolled at the current dose level to confirm MTD. If one of the first 3 patients treated at a given dose level develops a DLT during the first cycle of treatment, three additional patients will be enrolled onto the current dose level. If, at any time in the enrollment of these 3 additional patients, a patient develops a DLT, enrollment will be closed to this dose level. Enrollment will be re-opened to the next lower dose level if fewer than 6 patients have been treated at that dose level. If none of these 3 additional patients develops a DLT during the first cycle of treatment, enrollment to this dose level will be closed and enrollment will reopen at next higher dose level. If

there are no other higher dose levels to be tested, this will be considered the MTD.

Patients will return to the clinic every 28 days for physical exams, laboratory assessments and review of side effects.

Patients who do not have disease progression and have not experienced unacceptable toxicities will be eligible to continue protocol treatment at their current dose level until disease progression, unacceptable toxicity, or refusal. Those patients who have not experienced progression of disease but have unacceptable toxicity may be eligible for re-treatment at a lower dose.

Part 2: Dose Expansion Once the MTD has been established or determined, 4-10 additional patients will be treated at the MTD of lenalidomide and ibrutinib at the same schedule as above. Dexamethasone will be given at the same dose as in the dose escalation portion of the study.

Patients who have not had disease progression and have experienced acceptable toxicity will be eligible to continue protocol treatment at their current dose level until disease progression, unacceptable toxicity, or refusal. Those patients who have not progressed and who have experienced unacceptable toxicity may be eligible for re-treatment at a lower dose. A maximum of 2 reductions are allowed.

Criteria for discontinuation of protocol therapy include:

- Tumor progression
- Request by the patient to withdraw
- Unacceptable adverse events
- Treatment delay of >4weeks
- Intercurrent illness which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree that require discontinuation of drug
- Non-protocol chemotherapy, or an experimental drug during the trial

Patients who discontinue treatment for any of the above reasons will go to survival follow-up. Once a patient has entered the survival follow-up phase of the trial, his/her therapy is at the discretion of the treating physician. Patients' charts will be reviewed for progression and survival endpoints during visits with treating physicians.

Bone marrow aspirate will be collected at pre-treatment and at end of cycle 1 for micro-RNA profiling and gene expression for correlative studies.

Peripheral blood will be collected at pre-treatment, after cycles 1, 3, 6 and 12 for immunome correlative studies.

Inclusion Criteria	1. Men and women ≥ 18 years 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. 3. Symptomatic MM (as defined by revised IMWG criteria) with measurable disease, defined here as having at least one of the following: • Serum monoclonal protein ≥ 0.5 g/dL • ≥200 mg of monoclonal protein in the urine on 24 hour electrophoresis • Serum immunoglobulin free light chain: involved FLC ≥ 10 mg/dL (≥ 100 mg/L) AND abnormal serum immunoglobulin kappa to lambda free light chain ratio 4. At least 1 prior line of therapy with demonstrated disease progression following the most recent line of treatment (induction followed by maintenance or autologous transplant and maintenance, will be considered a line of therapy. Each subsequent change of regimen will be considered a line of therapy) 5. Progression of disease within 60 days of completion of last therapeutic regimen or the failure to achieve minimal response while on last treatment (according to IMWG). 6. Patients should not have progressed on lenalidomide at a dose of more than 10 mg. 7. No prior treatment with ibrutinib or any other protein kinase inhibitory drug or drug targeting the BCR signal transduction pathway. 8. Patients with prior Daratumumab and allogeneic stem cell transplant are included. 9. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN except if on anticoagulation for medical reasons in which case INR should be ≤3 10. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to registration, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin (which require at least 14 days prior to screening and enrollment) defined as: • Absolute neutrophil count (ANC) ≥1000/mm^3 independent of growth factor support. • Transfusion independent platelet counts ≥75,000/mm^3 (or ≥50,000/mm^3 if bone marrow involvement is ≥50%).

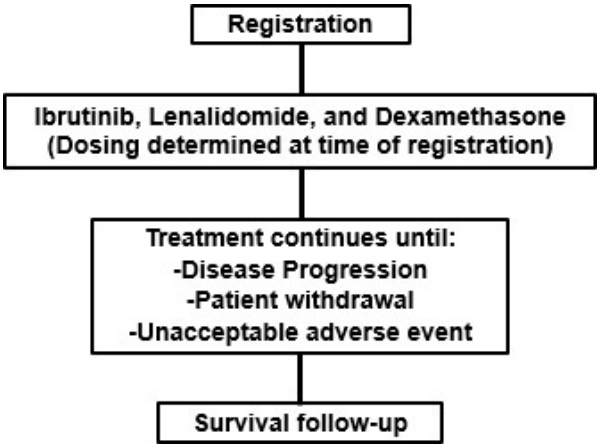
	• Hemoglobin level ≥8 g/dL, independent of transfusion support. 11. Biochemical values must be within the following limits within 7 days prior to registration • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN). • Total bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin). • Serum creatinine ≤2 x ULN or GFR ≥ 30 ml/min based on either the estimated Glomerular Filtration Rate (Crockcoft-Gault) or measured GFR from 24-hour urine sample. Study participants with 30 < GFR < 60 will be treated according to manufacturer's instruction with lenalidomide 10mg rather than 25 mg. 12. Ability to understand and willingness to sign a written informed consent from (ICF). 13. Ability to adhere with the study visit schedule and other protocol procedures. 14. A negative pregnancy test will be required for all women of child bearing potential within 7 days prior to study treatment start. Breast feeding is not permitted. 15. Fertility requirements • Female patients with child bearing potential must have a negative pregnancy test at least 7 days before starting treatment drugs. • Male subject must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential. • Female patients must be either post-menopausal, free from menses ≥2 yrs, surgically sterilized, willing to use two adequate barrier methods of contraception to prevent pregnancy or agree to abstain from sexual activity starting from screening and for 90 days afterwards. • Female patients of child bearing potential must agree to comply with the fertility and pregnancy test requirements dictated by the Rev-Assist program. 16. Willingness to provide blood and tissue samples for correlative research purposes

Exclusion Criteria	1. Prior history of Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, osteosclerotic myeloma, Crow-Fukase syndrome, primary amyloidosis or plasma cell leukemia. 2. Radiotherapy within 21 days of registration. However, if the radiation portal was localized to single lesion or fracture site and covered by ≤ 5% of the bone marrow reserve (by investigator estimate), the subject may be enrolled irrespective of the end date of radiotherapy. 3. Prior chemotherapy: • Alkylators (e.g. melphalan, cyclophosphamide) ≤21 days prior to registration and/or monoclonal antibody ≤ 6 weeks prior to first administration of study treatment. • Anthracyclines ≤21 days prior to registration. • High dose corticosteroids, immune modulatory drugs (thalidomide), or proteasome inhibitors (bortezomib or carfilzomib) ≤14 days prior to registration. o If patient is on current lenalidomide treatment, they may continue on current dose until starting protocol treatment. 4. No concomitant high dose corticosteroids (concurrent use of corticosteroids). EXCEPTION: Patients may be on chronic steroids (maximum dose 10 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, i.e., adrenal insufficiency, rheumatoid arthritis, etc. 5. Currently active, clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of registration, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification (QTcF> 470 msec). 6. Unable to swallow capsules or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, or complete bowel obstruction. 7. History of prior malignancy, with the exception of the following: • Malignancy treated with curative intent and with no known active disease present for more than 3 years prior to registration and felt to be at low risk for recurrence by treating physician;

	• Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease; or • Adequately treated breast or cervical carcinoma in situ without current evidence of disease. 8. Peripheral neuropathy Grade > 2 on clinical examination within 14 days prior to registration. 9. Uncontrolled diabetes mellitus. 10. Currently active systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment). 11. Use of antibiotics for treatment of infection within 14 days prior to registration. 12. Recent infection requiring systemic treatment that was completed within 14 days of registration. 13. Known infection with human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection. Note: Subjects with known history positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result within 14 days prior to registration. 14. History of stroke or intracranial hemorrhage within 6 months prior to registration. 15. Subjects who received a strong cytochrome P450 (CYP3A) inhibitor within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong CYP3A inhibitor see (Appendix II) 16. Currently active, clinically significant hepatic impairment. Child-Pugh class B or C according to the Child Pugh classification (Appendix III). 17. Lactating or pregnant. 18. Major surgery within 4 weeks prior to registration. 19. Known bleeding disorders (eg, von Willebrand's disease or hemophilia). 20. Allergies and adverse drug reactions: history of allergy to study drug components.

	21. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. 22. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 23. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 5.0), Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.

Schema


Registration
Ibrutinib, Lenalidomide, and Dexamethasone
(Dosing determined at time of registration)
Treatment continues until:
-Disease Progression
-Patient withdrawal
-Unacceptable adverse event
Survival follow-up

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1. Background Information

1.1. Overview of Disease and Patient Population

1.1.1 Overview of Disease

Multiple myeloma (MM) is the second most common hematological malignancy with approximately 22,000 new cases diagnosed each year in the United States. Prior to the availability of carfilzomib and pomalidomide, MM patients refractory to both lenalidomide and bortezomib had an event free survival of approximately 5 months and an estimated median overall survival of 9 months[1]. The median overall survival (OS) has been extended with the use of pomalidomide and carfilzomib to over 15 months[2]. However, all MM patients will eventually become resistant and new mechanisms of action are important to study and develop in order to continue to improve the OS of relapsed and refractory (RR) patients.

1.1.2 Lenalidomide

Lenalidomide (Revlimid®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. Its mechanism of action remains to be fully characterized. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro. Lenalidomide is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Lenalidomide in combination with dexamethasone is indicated for the treatment of newly diagnosed multiple myeloma patients and those who have received at least one prior therapy.

1.1.2.1 Clinical Experience in Relapsed Multiple Myeloma

A multicenter, open-label, randomized phase 2 study evaluated 2 doses of lenalidomide for relapsed, refractory multiple myeloma patients. Seventy patients were randomized to receive oral lenalidomide either 30 mg once-daily or 15 mg twice-daily for 21 days of every 28-day cycle. Patients with progressive or stable disease after 2 cycles received dexamethasone. Analysis showed an increased grade 3/4 myelosuppression in patients receiving 15 mg twice daily as compared to those receiving 30mg daily (41% versus 13%, P= .03). Responses were evaluated according to European Group for Blood and Marrow Transplantation (EBMT) criteria. Overall response rate (complete, partial, or minor) to lenalidomide alone was 25% (24% for once daily and 29% for twice-daily lenalidomide). Median overall survival (OS) in the 30-mg once-daily and twice-daily groups was 28 and 27 months, respectively. Median progression free survival was 7.7 months on once-daily versus 3.9 months on twice-daily lenalidomide (P = 0.2). Dexamethasone was added in 68 patients and 29% responded. Time to first occurrence of clinically significant grade 3 / 4 myelosuppression was shorter in the twice daily group (1.8 vs 5.5 months, P = .05). Significant peripheral neuropathy and deep vein thrombosis each occurred

in only 3%. Lenalidomide was active and well tolerated in relapsed, refractory myeloma, with the 30-mg once-daily regimen providing the basis for future studies as monotherapy and with dexamethasone[3].

In a safety and efficacy study of single agent lenalidomide in relapsed and refractory multiple myeloma patients, lenalidomide 30 mg (days 1-21 of 28-day cycle) was given to 222 patients who had relapsed or progressed after 1 or more prior therapies[4]. Sixty-seven percent of patients had received three or more prior therapies, and 45% had received one or more autologous stem cell transplant. Eighty and 43% of patients had received thalidomide and bortezomib based therapies respectively. The median dose of lenalidomide was 25 mg (5-30mg) and the median duration of treatment was 4.2 months (0.06-38). The overall response rate (complete and partial) was 26% with 2% complete response[4].

Two phase III trials comparing lenalidomide + dexamethasone to single agent dexamethasone in patients with relapsed and/or refractory multiple myeloma were published[5, 6]. Patients who had received 1-3 prior therapies, and progressed on their last therapy were randomized to receive lenalidomide 25 mg daily on days 1-21, placebo on days 22-28, plus dexamethasone, 40 mg, days 1-4, 9-12, and 17-20 of every 28 day cycle, or placebo daily for 28 days plus dexamethasone, 40 mg, days 1-4, 9-12, 17-20, every 28 days. The responses reported are summarized in Table 1 while the incidence of DVT and pulmonary embolism are summarized in Table 2. Anemia, thrombocytopenia, neutropenia, fatigue, neuropathy, and constipation were observed more often in the lenalidomide + dexamethasone group compared to the dexamethasone only group; however, these events were generally manageable.

Table 1 Response Rates in Phase III Trials of Relapse refractory MM

	Weber et al (NEJM 2007)			Dimopoulos et al (NEJM 2007)		
	Lenalidomide + Dexa (n=177)	Dexa Alone (n=176)	*P* Value	Lenalidomide + Dexa (n=176)	Dexa Alone (n=175)	*P* Value
Overall Response Rate (%)	108 (61)	35 (20)	<0.001	106 (60.2)	42 (24)	<0.001
Complete Response	14.1%	0.6%	<0.001	15.9%	3.4%	<0.001
Median TTP (mo.)	11.1	4.7	<0.001	11.3	4.7	<0.001
Median OS (mo.)	29.6	20.2	<0.001	Not Reached	20.6	0.03

Table 2 DVT & PE Risks in Phase III Trials of Relapse refractory MM

	Weber et al	Dimopoulos et al

	Lenalidomide + Dexamethasone	Dexamethasone Alone	Lenalidomide + Dexamethasone	Dexamethasone Alone
Deep Vein Thrombosis (%)	11.9	3.4	4.0	3.5
Pulmonary Embolism (%)	3.4	0.6	4.4	1.2

The dexamethasone used in the above two studies is considered high dose. A phase III study compared lenalidomide plus high-dose dexamethasone (doses and schedule as described above) to lenalidomide (dose and regimen as above) plus low-dose dexamethasone (40 mg given on days 1, 8, 15, 22 of 28-day cycles) in newly diagnosed multiple myeloma patients. Overall survival at 1 year was 96% for the low-dose dexamethasone compared to 87% for the high-dose dexamethasone (P=0.0002). As a result, the trial was stopped and patients on the high-dose therapy were crossed over to the low-dose therapy[7]. Subsequently, most therapies involving dexamethasone use low-dose.

1.1.2.2 Ibrutinib and Multiple Myeloma

Ibrutinib is a Bruton's tyrosine kinase (Btk) inhibitor. Btk is a member of the Tec family of tyrosine kinases, whose activation regulates B-cell development and plays an important role in antibody production and has been shown to be a therapeutic target in MM[8, 9]. Treatment of myeloma cells directly with ibrutinib results in a modest reduction in cell viability and induction of apoptosis in vitro. In addition, ibrutinib directly inhibits osteoclastic bone resorption, prevents release of multiple osteoclast-derived tumor growth factors, prevents adhesion of MM cells to bone marrow stromal cells (BMSCs), and inhibits migration of SDF-1-induced MM cells[10,11]. In addition, Ibrutinib has been shown to inhibit BTK-driven NK-kB p65 activity to overcome bortezomib-resistance[8, 11]. Dysregulation of osteoclast activity plays a critical role in MM pathogenesis. Btk regulates osteoclast differentiation through RANK signaling, and indeed in pre-clinical studies involving MM cells lines, inhibition of Btk decreased OC function. A phase II study of Ibrutinib single agent or in combination with dexamethasone in relapsed or relapsed/refractory MM showed a clinical benefit across all dose levels but the highest activity of 25% at the highest dose of 840 mg with or without 40mg dexamethasone without the occurrence of new safety signals[12]. The number of median prior therapies was 4 (range, 2-14), 41% had ≥ 5 prior therapies and 80% had undergone autologous stem cell transplants. Sixty-two percent of patients were refractory to their last line of therapy including 45% to both an immunomodulatory agent and a proteasome inhibitor. Overall, 57% experienced a Grade 3 or higher adverse event. The most commonly reported non-hematologic toxicities (any grade) were diarrhea (51%), fatigue (41%), nausea (35%), dizziness (25%), and muscle spasms (23%). The majority were Grade 1 and 2. Hematologic toxicity of any grade was anemia (29%), thrombocytopenia (23%), and neutropenia (7%) with 16%, 9% and 4% being Grade 3, respectively. There were no clinically meaningful differences among dose levels. At least one dose modification occurred in 22% of patients, with 6 discontinuing due to an adverse event[12].

1.1.2.3 Ibrutinib and Lenalidomide

The combination of Ibrutinib and lenalidomide have been studied in patients with relapsed and refractory lymphoma and chronic lymphocytic leukemia in a phase 1 and 2 clinical trials. The

phase 2 study in mantle cell lymphoma, a B-cell malignancy, as in MM was well tolerated with the most common grade 3-4 adverse events being neutropenia (38%), infection (22%) and cutaneous toxicity. The preclinical study in MM suggest synergism between lenalidomide and ibrutinib in MM[11]. A phase 1 / 2b clinical trial of Ibrutinib and pomalidomide (a third generation Imid) is currently ongoing (NCT02548962). The anti-myeloma effects of lenalidomide have been previously described and include caspase-8-dependent apoptosis of MM cells, inhibition of angiogenesis, and activation of NK and T effector cells. Both ibrutinib and lenalidomide downregulate IRF4, a master transcriptional factor that mediates myeloma cell survival, and both exert effects on the BM microenvironment with overlapping yet distinct targets that influence MM cell growth and survival. The combination of lenalidomide and ibrutinib is thus an attractive therapeutic strategy not only as a potent anti-MM regimen but also in terms of positively impacting bone disease.

1.1.3 Study Rationale

MM patients refractory to both lenalidomide and bortezomib have an event free survival of approximately 5 months and an estimated median overall survival of 9 months[1]. While this has improved with pomalidomide and carfilzomib to a median of 15 months, all MM patients will eventually become resistant and new mechanisms of action are important to study and develop in order to continue to improve the OS of relapsed and refractory (RR) patients. Ibrutinib, a Btk inhibitor, has shown efficacy as a single agent and in combination with dexamethasone. Pre-clinical studies suggest synergism between Ibrutinib and lenalidomide in MM cell lines.

We seek to determine the response in relapse/refractory multiple myeloma patients using Ibrutinib in combination with lenalidomide and dexamethasone with the primary endpoint of determining safety, tolerability and the maximum tolerated dose (MTD), and secondary endpoints of progression-free survival, overall survival, duration of response, and pharmacokinetic and pharmacodynamics of Ibrutinib in combination with lenalidomide and dexamethasone.

1.2. Study Design

This is a single-arm, open label, phase Ib study of Ibrutinib in combination with lenalidomide and dexamethasone in adult (age 18 years and older) patients with relapsed/refractory MM. A dose-escalation will be completed with the primary endpoint of determining safety, tolerability and maximum tolerated dose (MTDs) in a standard 3+3 design over 3 dose levels of 560, 560 and 840 mg of Ibrutinib given orally daily, lenalidomide given at 15 mg, 25 mg and 25 mg orally daily on days 1-21 of a 28-day cycle and dexamethasone 40 mg given orally weekly (patients 75 yrs and older will start with Dexamethasone20 mg) (Table 3 and 4). Patients with GFR 30-60 ml/min will receive lenalidomide 10 mg daily, days 1 – 21 of 28 according to manufacturer's recommendation. A minimum of 6 and a maximum of 18 patients will be recruited in the phase I portion. Upon identification of the MTD for the dose level combination of Ibrutinib and lenalidomide/dexamethasone, a 10-patient expansion cohort will commence. Secondary endpoints of progression-free survival, overall survival, duration of response, and pharmacokinetic and pharmacodynamics of Ibrutinib in combination with lenalidomide and dexamethasone will be assessed.

Please see Section 7 for dexamethasone dose modification guidelines.

Table 3 Dose Level

	Ibrutinib	Lenalidomide	Dexamethasone[a]
1 (starting dose)	560 mg	15 mg	40mg
2	560mg	25 mg	40mg
3	840mg	25 mg	40mg

[a] The starting dose of dexamethasone will be reduced to 20 mg based on tolerability or if the patient is 75 years or older at the time of registration.

Table 4 Dosing Schedule

Agent	Dose	Route	Days	ReRx
Ibrutinib	assigned at time of registration	Oral	1-28	Every 28 days
Lenalidomide	assigned at time of registration	Oral	1-21	
Dexamethasone	40 mg if age < 75 years old at registration	Oral	1,8,15, 22	
	20 mg if age ≥75 years old at registration			

Please see section 7.1 for the definition of Dose Limiting Toxicity (DLT) occurring during combination of lenalidomide, dexamethasone and Ibrutinib.

Determination of Maximum Tolerated Dose (MTD)

The maximum tolerated dose is defined as the highest dose level among those tested where at most 1 out of 6 patients develops a DLT prior to the start of their second cycle of treatment and the next highest dose level is such that 2 or more out of a maximum of 6 patients treated at this dose level developed a DLT prior to the start of their second cycle of treatment.

Enrollment and determination of MTD

A minimum of 2 or a maximum of 6 patients will be accrued to a given dose level. Doses will not be escalated in any individual patient. If none of the first 3 patients treated at a given dose level develops a DLT during the first cycle of treatment, enrollment to the dose level will be closed and enrollment will reopen at next higher dose level. If there are no other higher dose levels to be tested, three additional patients will be enrolled at the current dose level to confirm MTD. If one of the first 3 patients treated at a given dose level develops a DLT during the first cycle of treatment, three additional patients will enroll onto the current dose level. If, at any time in the enrollment of these 3 additional patients, a patient develops a DLT, enrollment will be closed to this dose level. Enrollment will be re-opened to the next lower dose level if fewer than

6 patients have been treated at that dose level. If none of these 3 additional patients develops a DLT during the first cycle of treatment, enrollment to this dose level will be closed and enrollment will reopen at next higher dose level. If there are no other higher dose levels to be tested, this will be considered the MTD.

For this protocol, the patient must return to their registration institution for evaluation and continuation of treatment (at least every 28 ± 3 days) according to the test schedule. Patients who have not had disease progression and have experienced acceptable toxicity will be eligible to continue protocol retreatment at their current dose level until disease progression, unacceptable toxicity, or refusal. Those patients who have not progressed and who have experienced unacceptable toxicity may be eligible to continue protocol retreatment at a lower dose.

Criteria for discontinuation of all protocol therapy include:

- Tumor progression
- Request by the patient to withdraw
- Unacceptable adverse events
- Treatment delay of >4weeks
- Intercurrent illness which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree of require discontinuation of drug
- Non-protocol chemotherapy, or an experimental drug during the trial

Patients who discontinue treatment for any of the above reasons will go to survival follow-up. Once a patient has entered the survival follow-up phase of the trial, his/her therapy is at the discretion of the treating physician. The sponsor would like to collect that information, if the patient agrees.

Patients who discontinue treatment due to toxicity should be monitored until resolution or stabilization of adverse event.

Expansion cohort

Once the MTD has been established or determined, 10 additional patients will be treated at the MTD. The total number of patients to be enrolled in the study will be 28.

1.3. Study Design Rationale

In the last decade, significant progress has been made in the treatment of Multiple Myeloma (MM), primarily due to the introduction of proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs). However, nearly all patients ultimately relapse and require further therapy, making the development of new compounds for MM therapy an important priority.

Preclinical studies suggest synergism between lenalidomide and ibrutinib in MM. The anti-myeloma effects of lenalidomide have been previously described and include caspase-8-dependent apoptosis of MM cells, inhibition of angiogenesis, and activation of NK and T effector cells. Both ibrutinib and lenalidomide downregulate IRF4, a master transcriptional factor that mediates myeloma cell survival, and both exert effects on the BM microenvironment with overlapping yet distinct targets that influence MM cell growth and survival. The combination of lenalidomide and ibrutinib is thus an attractive therapeutic strategy not only as a potent anti-MM regimen, but also in terms of positively impacting bone disease.

Based on these preliminary results, we propose a phase Ib study to determine the dosing schedule

of Ibrutinib in combination with lenalidomide and dexamethasone, and to assess the clinical efficacy of this combination.

1.4. Study Agents

1.4.1 Ibrutinib

Ibrutinib (Imbruvica®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development, LLC for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the US and EU, for patients with mantle cell lymphoma (MCL) who have received one prior line of therapy and first-line treatment for chronic lymphocytic leukemia (CLL), first-line treatment of patients with CLL with a deletion of the short arm of chromosome 17 (del17p) or a TP53 mutation, and patients with Waldenström's macroglobulinemia. Ibrutinib is currently under investigation in various indications as a single agent and in combinations.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigens. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways[20].

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

1.4.1.1 Summary of Nonclinical Data

Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk[27]. In vitro, ibrutinib is a potent inhibitor of BTK activity (IC50 = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression[24].

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current ibrutinib Investigator's Brochure.

Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues

(lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 20 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily and 420 mg, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

1.4.1.2 Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

Pharmacokinetics and Product Metabolism

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

For the most up to date and comprehensive pharmacokinetics (PK) and product metabolism information regarding ibrutinib, please refer to the current IB.

Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided

in below. For the most up to date and most comprehensive safety information regarding ibrutinib, please refer to the current version of the IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

Pooled safety data for a total of 1318 subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis or final analysis as of the 31 May 2016 cutoff date for the current IB update in B-cell malignancies are summarized below.

Table 5 Most frequently reported treatment-emergent adverse events (TEAEs)

Most frequently reported TEAEs >15%	Most frequently reported Grade 3 or 4 TEAEs >3%	Most frequently reported Serious TEAEs >2%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
	Diarrhea	
Pyrexia	Atrial fibrillation	
Neutropenia		
Upper respiratory tract infection		
Thrombocytopenia		
Edema peripheral		

For more detailed information refer to the current version of the IB.

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

Table 6 Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423)

Most frequently reported TEAEs >20%	Most frequently reported Grade 3 or 4 TEAEs >3%	Most frequently reported Serious TEAEs >2%
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Hypertension	
Pyrexia	Anemia	
	Fatigue	
	Diarrhea	

For more detailed information refer to the current version of the IB.

1.4.2 Risks

1.4.2.1 Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, subdural intracranial hemorrhage, and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 6.4.2 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4.4 for guidance on ibrutinib management with surgeries or procedures. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed.

1.4.2.2 Lymphocytosis and Leukostasis

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/µL) may confer increased risk. For subject and ibrutinib management guidance, refer to Section 5.

Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5000/µL), often associated with reduction of lymphadenopathy, has been observed in most subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (increase in the number of circulating

lymphocytes eg, >400,000/μL) is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy and typically resolves within a median of 8.0 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. This pharmacodynamic effect was less prominent or not observed in other indications.

1.4.2.3 Infections

Infections (including sepsis, bacterial, viral or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 6.4.1). (Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.4.2.4 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding.

1.4.2.5 Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 7).

1.4.2.6 Non-Melanoma Skin Cancer

Non-melanoma skin cancers have occurred in patients treated with ibrutinib. Patients should be monitored for the appearance of non-melanoma skin cancer.

1.4.2.7 Tumor Lysis Syndrome

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

1.4.2.8 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Dose modification guidelines for severe or prolonged symptoms related to diarrhea can be found in Section 8.

1.4.2.9 Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens - Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticaria, and angioedema have been reported.

1.4.2.10 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 8).

1.4.2.11 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor patients for new onset of hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.4.3 Lenalidomide (Revlimid)

Lenalidomide is approved for use in MM and its toxicity profile is well known. Please refer to the current version of the IB.

2. Objectives and Endpoints

2.1. Primary Objectives

The primary objectives of this study are:

1. To determine the maximum tolerated dose (MTD)-recommended phase II doses of ibrutinib in combination with lenalidomide and dexamethasone
2. To examine the safety profile of ibrutinib in combination with lenalidomide and dexamethasone

2.2. Secondary Objectives

The secondary objectives of this study are:

1. To determine progression-free survival (PFS)
2. To determine overall survival (OS)
3. To determine duration of response
4. To determine overall response rate (ORR)

2.3. Exploratory Objectives

The correlative objective of this study is to:

1. To perform select immunologic studies with this combination

2.4. Endpoints

2.4.1 Primary and Secondary

Primary:

1. Maximum tolerated dose (MTD): The maximum tolerated dose (MTD) is defined as the highest dose level among those under consideration where at most 1 of 6 patients develops a dose limiting toxicity and 2 or more of the 3-6 patients treated at the next higher dose level develop a dose limiting toxicity.
2. Safety profile: The maximum grade of each type of toxicity will be recorded for each patient. For each toxicity reported by dose level, the percentage of patients developing any degree of that toxicity as well as the percentage of patients developing a severe degree (Grade 3 or higher) due to treatment will be determined.

Secondary:

1. Progression free survival (PFS) defined as the time from study entry to the documentation of disease progression using IMWG criteria or death due to any cause.
2. Overall survival (OS) is defined as time from registration to death due to any cause.
3. Overall Response rate(ORR)
4. Duration of response, defined as the time from documented response to disease progression among those patients whose disease meets the IMWG criteria for disease response.
5. Safety Profile: CTCAE v5.0 will be used to grade and assign attribution to each adverse event reported.

2.4.2 Correlative

1. Immunologic studies: bone marrow aspirate and peripheral blood samples will be collected from patients for immunome studies. See Protocol Section 13 for more information.

3. Patient Selection / Population

19-25 patients (9-18 dose escalation; 4-10 dose expansion) with symptomatic multiple myeloma (as defined by IMWG criteria) will be enrolled across multiple investigational sites in the United States. Screening labs must be performed within 7 days prior to registration. Complete body CT scan if clinically indicated at screening must be performed within 14 days prior to registration.

3.1. Inclusion Criteria

1. Men and women ≥ 18 years
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (Appendix I).
3. Symptomatic MM (as defined by revised IMWG criteria) with measurable disease, defined here as having at least one of the following:
    - Serum monoclonal protein ≥ 0.5 g/dL
    - ≥200 mg of monoclonal protein in the urine on 24 hour electrophoresis

- Serum immunoglobulin free light chain: involved FLC ≥ 10 mg/dL (≥ 100 mg/L) AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.

4. At least 1 prior therapy with demonstrated disease progression following the most recent line of treatment.
5. Progression of disease within 60 days of completion of last therapeutic regimen or the failure to achieve minimal response while on last treatment (according to IMWG).
    - Patients should not have progressed on lenalidomide at a dose of more than 10 mg.
6. No prior treatment with ibrutinib or any other protein kinase inhibitory drug or drug targeting the BCR signal transduction pathway.
7. Patients with prior daratumumab and allogeneic stem cell transplant are included.
8. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN, except if on anticoagulation for medical reasons in which case INR should be ≤ 3
9. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to registration, with the exception of pegylated G-CSF (pegfilgrastim) and darbopoeitin which require at least 14 days prior to screen and enrollment defined as:
    - Absolute neutrophil count (ANC) ≥1000/mm^3 independent of growth factor support.
    - Transfusion independent platelet counts ≥75,000/mm^3 (or ≥50,000/mm^3 if bone marrow involvement is ≥50%).
    - Hemoglobin level ≥8 g/dL, independent of transfusion support.
10. Biochemical values must be within the following limits within 7 days prior to registration
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN).
    - Total bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin).
    - Serum creatinine ≤2 x ULN or GFR ≥ 30 ml/min based on either the estimated Glomerular Filtration Rate (Crockcoft-Gault) or measured GFR from 24-hour urine sample. Study participants with GFR 30-50 ml/min will be treated according to manufacturer's instruction with lenalidomide 10mg rather than 25 mg.
11. Ability to understand and willingness to sign a written informed consent form (ICF).
12. Ability to adhere with the study visit schedule and other protocol procedures.
13. A negative pregnancy test will be required for all women of child bearing potential within 7 days prior to registration. Breast feeding is not permitted.
14. Fertility requirements
    - Female patients with child bearing potential must have a negative pregnancy test at least 7 days before starting treatment drugs.
    - Male subject must use an effective barrier method of contraception during the study and for 3 months following the last dose if sexually active with a female of childbearing potential.

- Female patients must be either post-menopausal, free from menses ≥ 2yrs, surgically sterilized, willing to use two adequate barrier methods of contraception to prevent pregnancy, or agree to abstain from sexual activity starting from screening and for 90 days after lenalidomide treatment
- Female patients of childbearing potential must agree to comply with the fertility and pregnancy test requirements dictated by the Rev-Assist program.

15. Willingness to provide blood and tissue samples for correlative research purposes

3.2. Exclusion Criteria

1. Prior history of: Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome, osteosclerotic myeloma, Crow-Fukase syndrome, primary amyloidosis or plasma cell leukemia.
2. Radiotherapy within 21 days of registration. However, if the radiation portal was localized to single lesion or fracture site and covered by ≤ 5% of the bone marrow reserve (by investigator estimate), the subject may be enrolled irrespective of the end date of radiotherapy.
3. Prior chemotherapy:
    - Alkylators (e.g. melphalan, cyclophosphamide) ≤21 days prior to registration and/or monoclonal antibody ≤ 6 weeks prior to first administration of study treatment.
    - Anthracyclines ≤21 days prior to registration.
    - High dose corticosteroids, immune modulatory drugs (thalidomide), or proteasome inhibitors (bortezomib or carfilzomib) ≤14 days prior to registration.
        - If patient is on current lenalidomide treatment, they may continue on current dose until starting protocol treatment.
4. No concomitant high dose corticosteroids (concurrent use of corticosteroids). EXCEPTION: Patients may be on chronic steroids (maximum dose 10 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, i.e., adrenal insufficiency, rheumatoid arthritis, etc.
5. Currently active, clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration or baseline QTcF of > 470.
6. Unable to swallow capsules or disease significantly affecting gastrointestinal function, such as malabsorption syndrome, resection of the stomach or small bowel, or complete bowel obstruction.
7. History of prior malignancy, with the exception of the following:
    - Malignancy treated with curative intent and with no known active disease present for more than 3 years prior to registration and felt to be at low risk for recurrence by treating physician;
    - Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease; or

- Adequately treated breast or cervical carcinoma in situ without current evidence of disease.

8. Peripheral neuropathy Grade > 2 on clinical examination within 14 days prior to registration.
9. Uncontrolled diabetes mellitus.
10. Currently active systemic fungal, bacterial, viral, or other infection not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).
11. Use of antibiotics for treatment of infection within 14 days prior to registration
12. Recent infection requiring systemic treatment that was completed within 14 days of registration.
13. Known infection with human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.
    Note: Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result within 14 days prior to registration.
14. History of stroke or intracranial hemorrhage within 6 months prior to registration.
15. Patients who received a strong cytochrome P450 (CYP) 3A inhibitor within 7 days prior to the first dose of ibrutinib or patient who requires continuous treatment with a strong CYP3A inhibitor (Appendix II).
16. Currently active, clinically significant hepatic impairment (Child-Pugh class B or C) according to the Child Pugh classification (Appendix III).
17. Lactating or pregnant
18. Major surgery within 4 weeks prior to registration
19. Known bleeding disorders (e.g. von Willebrand's disease or hemophilia).
20. Allergies and adverse drug reactions: history of allergy to study drug components
21. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
22. Any life-threatening illness, medical condition, or organ systemic dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
23. Unresolved toxicities from prior anti-cancer therapy, defined as not having resolved to CTCAE Version 5.0, Grade 0 or 1, with the exception of alopecia.

3.3. Inclusion of Women and Minorities

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

4. Site Enrollment Requirements

Site must submit all required essential documents including:

- IRB/Regulatory Approval of protocol, informed consent document and study participant materials obtained in one of two ways:
    - Option 1: use the Alliance Foundation Trials (AFT) Central IRB as the study site's IRB of record for this study [AFT will be using Quorum as the CIRB vendor for this study] **–OR-**

  - Option 2: Submit protocol to site institutional IRB
- Site Principal Investigator FDA Form 1572 and Curriculum Vitae
- Medical License
- Investigator's Protocol Signature Page
- Documentation of ICH Good Clinical Practice (ICH/GCP)
- Investigator Brochure Acknowledgement(s)

Essential documents must be submitted to the AFT electronic Trial Master File, accessible via the AFT website, [redacted] Sites will receive site selection correspondence with detailed requirements for site activation.

5. Patient Enrollment

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and enrollment.

Patients with impaired decision-making capacity may be enrolled on this study, where institutional policy and IRB of record allow.

Patient enrollment will be facilitated using the RAVE EDC system.

Patient must be enrolled prior to submission of biospecimens. Prior to accessing EDC, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent from and HIPAA authorization form

The RAVE-EDC system will provide the site with a confirmation of enrollment and treatment information. Please retain this confirmation for your records.

After written informed consent has been obtained, the study site will obtain a unique patient identifier by entering the patient into the patient enrollment system. The patient identifier will stay the same throughout the entire study. Patients must receive this identifier prior to submission of biospecimens.

6. Treatment Plan

6.1. Treatment Regimen

At the time of registration, the dose level of Ibrutinib and Lenalidomide will be assigned to the patient. The dose levels being examined in this study are presented in the following table:

Table 7 Dose levels for Ibrutinib, Lenalidomide and Dexamethasone

Dose Level	Ibrutinib	Lenalidomide	Dexamethasone[a]
1 (starting dose)	560 mg	15 mg	40mg

2	560mg	25 mg	40mg
3	840mg	25 mg	40mg

a The starting dose of dexamethasone will be reduced to 20 mg based on tolerability or if the patient is 75 years or older at the time of registration.

Table 8 Treatment Plan

Agent	Dose	Route	Days	ReRx
Ibrutinib	assigned at time of registration	Oral	1-28	Every 28 days
Lenalidomide	assigned at time of registration	Oral	1-21	
Dexamethasone	40 mg if age < 75 years old at registration	Oral	1, 8,15, 22	
	20 mg if age ≥75 years old at registration			

Treatment days are based on 28-day cycles. Patients will be treated on an outpatient basis. Refer to Protocol Section 11.0 for expected toxicities of study agents.

Please refer to Section 6.1 for dose escalation guidelines for ibrutinib.

6.2. Pre-Treatment Criteria

A treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1,000/μL;
- The platelet count is ≥ 50,000/μL;
- Any Ibrutinib or lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ grade 1 severity;
- Any other Ibrutinib or lenalidomide-related adverse event that may have occurred has resolved to ≤ grade 2 severity.

Laboratory values (excluding Child Pugh score) on Cycle 1, Day 1 must meet eligibility criteria per Section 3.1 (Inclusion Criteria).

6.2.1 Cycle 1 Day 1

Cycle 1 Day 1 hematology and chemistry laboratory assessments will be repeated if not performed within 7 days of starting study treatment.

6.2.2 Subsequent Cycles

Refer to dose modifications sections (Section 7) for re-treatment criteria on Day 1 of subsequent cycles.

6.3. Agent Administration

6.3.1 Ibrutinib

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

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

The first dose of ibrutinib will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Study drug may not be shipped to the subject without approval from PCYC and may not be dispensed to anyone other than the subject. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit. Returned capsules must not be redispensed to anyone.

6.3.1.1 Overdose

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

Refer to Section 11for further information regarding AE reporting.

6.3.2 Lenalidomide

Lenalidomide is a commercially available agent that is FDA approved for this indication. Administration of lenalidomide may be per package insert, institutional standard, or investigator discretion.

6.3.3 Dexamethasone

Dexamethasone is a commercially available agent that is FDA approved for this indication. Administration of dexamethasone may be per package insert, institutional standard, or investigator discretion.

6.3.4 Compliance

Patients should be instructed to record daily administration of the study drugs in a drug or medication diary.

6.4. Supportive Care and Concomitant Medications

6.4.1 Permitted Concomitant Medications

- **Anti-diarrheal medications:** Diarrhea can be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).
    - In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.
    - If diarrhea is severe (requiring intravenous rehydration) and/or associated fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.
- Transfusions of blood products may be given in accordance with institutional policy.
- DVT prophylaxis: patients will be required to be on some form of anticoagulation with at least aspirin 81 mg daily while on lenalidomide.
- Low dose oral corticosteroid of short courses (≤14 days) of treatment for non-cancer related medical reasons (e.g. joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 10 mg per day of prednisone or equivalent are permitted.
- Usage of antimicrobial prophylaxis in accordance with standard practice (eg, ASCO guidelines [Flower 2013]) is permitted and should be considered in subjects who are at increased risk for opportunistic infections.
- Corticosteroid for treatment of autoimmune cytopenias for <14 days at doses that do not exceed 100 mg per day of prednisone or equivalent are permitted.
- Localized palliative radiation therapy may be given for pain control. This will however need to be approved by study chairs. In addition, if there is any other situation in which radiation is required in the course of study therapy for an event that does not constitute disease progression, radiation may be administered as long as lenalidomide and ibrutinib are restarted immediately following radiation therapy.
- Neutrophil growth factors:
    - The use of filgrastim and pegfilgrastim or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Neutrophil growth factors are not allowed during cycle 1 in the course of DLT assessment.

6.4.2 Medications to be Used with Caution

6.4.2.1 CYP3A – Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and therefore strong

CYP3A inhibitors should be avoided.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, cobicistat and posaconazole) must be used, reduce ibrutinib dose to 140 mg for the duration of the inhibitor use or withhold ibrutinib treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) is indicated, reduce ibrutinib to 140 mg for the duration of the inhibitor use.
- Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 6.3.1).
- No dose adjustment is required in combination with mild inhibitors.
- Avoid concomitant use of systemic strong CYP3A inducers (eg. Carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix II. A comprehensive list of inhibitors, inducers and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/.

This website is continually revised and should be checked frequently for updates.

For the most comprehensive effect of CYP3A inhibitors or inducers of ibrutinib exposure, please refer to the current version of the IB.

6.4.2.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

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

6.4.2.3 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. Bleeding events of any grade, including bruising and petechiae, occurred in subjects with ibrutinib. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending on the type of surgery and the risk of bleeding.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation) should be monitored closely for signs and symptoms of bleeding and the risks and benefits of

continuing ibrutinib treatment.

6.4.3 Prohibited Concomitant Medications

Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy are prohibited while the subject is receiving protocol treatment. Radiation given for palliation of pain is allowed and is not considered protocol therapy violation. However, approval should be given by the chairpersons of the study.

Erythropoietic growth factors (eg, erythropoietin and darbepoetin) and neutrophil growth factors (eg, filgrastim and peg-filgrastim) are also prohibited during initial treatment, DLT assessment period.

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib.

6.4.4 Guidelines for Ibrutinib Management with Surgeries or Procedure

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

6.4.4.1 Minor Surgical Procedures

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

6.4.4.2 Major Surgical Procedures

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

7. Dose De-Escalation

7.1. Definition of Dose-Limiting Toxicity (DLT)

Attributions should be made as possibly, probably, or definite.

Table 9 Dose limiting toxicities (DLT)

Toxicity	***DLT Definition***
Hematologic	Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding or requirement for platelet transfusion.

	Grade 4 neutropenia lasting more than 5 days.
Other nonhematologic*	≥ grade 3 as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0*
	Grade 4 febrile neutropenia
	≥ grade 3 hyperglycemia due to dexamethasone if it cannot be controlled with appropriate therapy
	Treatment delays ≥ 21 days for any non-hematologic or hematological toxicity
	Treatment related death
	Grade ≥ 3 thrombotic/embolic events including DVT
	Grade 4 nausea, vomiting and diarrhea

*except grade 3 nausea, vomiting, diarrhea that does not require tube feeding, total parenteral nutrition or prolonged hospitalization, diarrhea responsive to medical treatment, nausea or vomiting controlled with antiemetics, or transient electrolyte abnormalities that resolve < grade 1 within 48 hours

7.2. Determination of Maximum Tolerated Dose (MTD)

The maximum tolerated dose is defined as the highest dose level among those tested where at most one out of 6 patients develops a DLT prior to the start of their second cycle of treatment and the next highest dose level is such that 2 out of a maximum of 6 patients treated at this dose level developed a DLT prior to the start of their second cycle of treatment.

7.3. Enrollment and determination of MTD

A minimum of 2 or a maximum of 6 patients will be accrued to a given dose level. Enrollment will begin with 3 patients accrued to dose level 1.

Dose de/escalation scheme for Dose 1:

- If none of the first 3 patients treated at dose level 1develops a DLT during the first cycle of treatment, then the next cohort of 3 patients will be enrolled at dose level 2.
- If one of the first 3 patients treated at dose level 1develops a DLT during the first cycle of treatment, then an additional cohort of 3 patients will be enrolled at the current dose level.
- If at most 1 of the 6 patients enrolled at dose level 1 develops a DLT during the first cycle of treatment, the next cohort of 3 patients will be treated at dose level 2.
- If 2 or more of the 6 patients enrolled at level 1 develops a DLT during the first cycle of treatment, enrollment will be halted, and the study team will discuss whether to

submit an amendment to reopen enrollment to a lower dose level.-

As of October 7, 2021, 3 patients have been enrolled onto dose level 2.

Dose de/escalation scheme for Dose 2:

- If none of the first 3 patients treated at dose level 2 develops a DLT during the first cycle of treatment, then the next cohort of 3 patients will be enrolled onto dose level 3.
- If one of the 3 patients treated at dose level 2 develops a DLT during the first cycle of treatment, then the next cohort of 3 patients will be enrolled at dose level 2.
    - If 2 or more of the 6 patients treated at dose level 2 develops a DLT then an additional 10 patients will be enrolled onto dose level 1 before completing enrollment.
- If 2 or more of 3 patients treated at dose level 2 develops a DLT during the first cycle of treatment, an additional 10 patients will be enrolled onto dose level 1 to further assess safety before completing enrollment.

Dose de/escalation scheme for Dose 3 (if applicable):

- If at most 1 of 6 patients treated at dose level 2 develops a DLT during the first cycle of treatment and 1 or fewer of the 6 patients treated at dose level 3 develops a DLT in the first cycle of treatment, then an additional 4 patients will be treated on dose level 3 before completing enrollment.
- If at most 1 of 6 patients treated at dose level 2 develops a DLT during the first cycle of treatment and 2 or more of the 3-6 patients treated at dose level 3 develops a DLT during the first cycle of treatment, then an additional 7 patients will be enrolled onto dose level 2 before completing enrollment.
- If at most 1 of 6 patients treated at dose level 3 develops a DLT during the first cycle of treatment then an additional 4 patients will be enrolled onto dose level 3 before completing enrollment.
- If 2 or more of the 3-6 patients treated at dose level 3 develops a DLT during the first cycle of treatment then an additional 7 patients will be enrolled onto dose level 2 before completing enrollment.

8. Dose and Treatment Modifications

8.1. Ibrutinib Dose/Delays Modifications

8.1.1 Dose Modification for Adverse Reactions

The dose of ibrutinib must be modified according to the dose modification guidelines in the tables below if any of the following toxicities occur:

- Grade 4 neutropenia (ANC <500/ μL) for more than 7 days. See Section 5.4 for instructions regarding the use of growth factor support.
- Grade 3 thrombocytopenia (platelets <50,000/ μL) in the presence of clinically

significant bleeding events

- Grade 4 thrombocytopenia (platelets <25,000/ μL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For grade 3 and above cardiac arrhythmias, ibrutinib should be held. For grade 2 and above heart failure, ibrutinib should be held. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation.

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

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 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

[redacted]

Table 10 Hematologic and Non-Hematologic Adverse Events

Occurrence	**Action to be Taken**
First	Hold Ibrutinib for Grade ≥3 neutropenia with infection/fever, or any Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib may be reinitiated. If these toxicities persist or recur following two dose reductions, ibrutinib will be discontinued
Non-Hematologic Adverse Events	
Occurrence	**Action to be Taken**
	Hold ibrutinib for Grade 2 cardiac failure. Hold Ibrutinib for any Grade 3 or greater non-hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline, ibrutinib may be reinitiated. If these toxicities persist or recur following two dose reductions, ibrutinib will be discontinued

Table 11 Ibrutinib Dose Reduction Levels

Starting Dose Level	840 mg	560 mg	420 mg
Dose Reduction Level 1	560 mg	420 mg	280 mg
Dose Reduction Level 2	420 mg	280 mg	140 mg
Dose Reduction Level 3	280 mg	140 mg	Discontinue
Dose Reduction Level 4	140 mg	Discontinue	N/A

8.1.1.1 Leukocytosis/Leukostasis (Optional for ibrutinib Monotherapy study)

A high number of circulating white blood cells (> 400,000/µL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukophoresis as indicated. Ibrutinib may be temporarily held, and medical monitor should be contacted.

8.1.2 Dose Modification for Hepatic Impaired Subjects

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

- For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose has to be adjusted to a level of 280 mg daily.
- For subjects who develop mild hepatic impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo is to a level of 280 mg daily.
- For subjects who develop moderate to severe hepatic impairment while on study (Child-Pugh class B and C)
- Study drug will be held until resolved to mild impairment (Child-Pugh class A)

Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines.

Table 12 Dose Modification Guidelines for Hepatic Toxicity

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

Points	Class
5-6	A
7-9	B

10-15	C

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . "Transection of te oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.

8.2. Lenalidomide, ibrutinib, and dexamethasone dose delay modifications

If treatment is held for more than 28 days, then all study treatment will be discontinued

Table 13 Lenalidomide, ibrutinib, and dexamethasone dose delay modifications

Neutropenia	Grade 3 or greater on day 1 of cycle: ~~h~~old lenalidomide and monitor CBC weekly; if resolves to ≤ grade 2 within 4 weeks, resume lenalidomide with 5mg dose reduction. During treatment, G-CSF or GM-CSF may be used after completion of cycle 1 for neutropenia at the discretion of as needed by the treating physician.
Febrile Neutropenia	Hold lenalidomide for the remainder of the cycle. Following completion of cycle 1, consider G-CSF administration until there is adequate count recovery ANC≥1000/μL + absence of fever. If neutropenia resolves ≤ grade 2, resume with lenalidomide at 5 mg dose reduction for subsequent cycles
Thrombocytopenia	If grade 3 or greater, hold lenalidomide the remainder of the cycle and until platelets ≥ 50,000/μL. Then resume lenalidomide at 5 mg dose reduction for subsequent cycles Platelet transfusion may be given following completion of cycle 1. Platelet transfusion for severe thrombocytopenia may be administered in cycle 1 at investigator discretion following discussion with Principal Investigators.
Anemia	For grade 3 or greater, hold lenalidomide for the remainder of the cycle and until hemoglobin recovers to ≤ grade 2. Red cell transfusion may be given.
Fatigue (asthenia, malaise)	For intolerable grade 2 or grade 3-4, hold protocol therapy thought to be probable or definitely related to the reaction until resolves to ≤ grade 1, then resume protocol therapy with dose reduction of implicated protocol therapy by one dose level (5 mg for lenalidomide, 1 dose level below for Ibrutinib and/or 50% for dexamethasone).
Rash	If grade 3 hold lenalidomide and ibrutinib until resolves to ≤ grade 2, then resume protocol therapy. Antihistamine (Benadryl, Claritin, zyrtec) may be given. If grade ≥ 3 rash recurs, hold therapy until rash resolves to ≤ grade 2, resume with one level dose reduction of agent(s) believed to be responsible for rash. For grade 4 rash, exfoliative or bullous rash, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), permanently discontinue lenalidomide
Renal insufficiency	For patients with calculated or measured GFR <30ml/min, lenalidomide should be omit until creatinine returns to baseline
Hepatic Toxicity	If Grade ≥ 2, hold lenalidomide. After return to baseline, restart at 1 dose level below.

Venous Thromboembolism	All protocol treatment should be held until the patient is adequately anti-coagulated. Patients with recurrent thrombosis despite adequate anti-coagulation should be removed from protocol therapy.
Suspected Pregnancy	Protocol therapy should be held until pregnancy is ruled out. Discontinue all protocol therapy if pregnancy is positive
Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 50%
Acute pancreatitis	Hold all study therapy until resolution. Do not resume dexamethasone. Consider one level dose reduction of either lenalidomide and/or ibrutinib.
Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed and decrease dexamethasone dose by 50%; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction. Permanently discontinue lenalidomide for any episode of Angioedema
Confusion or mood alteration > Grade 2 (interfering with function ± interfering with activities of daily living)	Hold all study therapy until symptoms resolve. Restart with 50% reduction of dexamethasone. If symptoms persist despite above measures, permanently discontinue dexamethasone. Consider one level dose reduction of lenalidomide and/or ibrutinib if either agent is felt to be contributing.
Muscle weakness > Grade 2 (symptomatic and interfering with function ±interfering with activities of daily living)	Hold all study therapy. Restart with 50% dose reduction of dexamethasone dose. If weakness persists despite above measures decrease dose by another 50%. Discontinue dexamethasone and do not resume if symptoms persist. Consider one level dose reduction of lenalidomide and/or ibrutinib if either agent is felt to contributing.
Hyperglycemia > Grade 3 or higher	Hold dexamethasone. Treat with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 50%.

8.2.1 Ibrutinib Dose Modifications for Use with CYP3A Inhibitors

The coadministration of ibrutinib with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of ibrutinib are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors.

Table 14 Recommended dose modifications for ibrutinib

Patient Population	Coadministered Drug	Recommended Ibrutinib Dose
B-Cell Malignancies	• Moderate CYP3A inhibitors	280 mg once daily Interrupt dose as recommended *(see label)*

	• Voriconazole 200 mg twice daily • Posaconazole suspension 100 mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily Interrupt dose as recommended *(see label)*
B-Cell Malignancies	• Posaconazole suspension 200 mg three times daily or 400 mg twice daily • Posaconazole IV injection 300 mg once daily • Posaconazole delayed-release tablets 300 mg once daily	70 mg once daily Interrupt dose as recommended *(see label)*
	• Other strong CYP3A inhibitors	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib

8.3. Criteria for Discontinuation of Protocol treatment

Patients are continued on treatment until any of the criteria for discontinuation of protocol therapy is met, which includes:

- Tumor progression
- Request by the patient to withdraw
- Unacceptable adverse events
- Treatment delay of >4weeks
- Intercurrent illness which would, in the judgment of the investigator, affect assessments of clinical status to a significant degree of require discontinuation of drug

Administration of non-protocol anti-tumor drug during the trial. Patients who discontinue treatment for any of the above reasons will go to survival follow-up where late toxicities and clinical outcome information will be collected every 6 months for a maximum of 2 years post registration. Once a patient has entered the survival follow-up phase of the trial, his/her therapy is at the discretion of the treating physician.

9. Study Assessments and Procedures

9.1. Assessment Types

9.1.1 Imaging Assessments

A CT/MRI scan will be collected if clinically indicated for all participants at screening (within 14 days prior to registration). A repeat scan will be collected if clinically indicated at completion of cycle 6 for patients with extramedullary disease indicated on the baseline scan.

9.1.1.1 Central Imaging Review

Scans should be submitted to Imaging Core Lab (ICL) at Ohio State University for central review within 3 days of acquisition.

The complete CT scans will be submitted to the Imaging Core Laboratory in digital DICOM format; BMP files, JPG files, or hard copies (films) are not acceptable.

The entire imaging data in DICOM format must be submitted to the ICL within no more than 30 business days once the image acquisition is completed at site.

De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the patient ID number and protocol number of the AFT trial. The de-identified digital images may be burned to a CD or transferred to a PC based system for further electronic data transfer purposes.

Data can be electronically transferred to the Imaging Core Lab by 1) Web Transfer; 2) FTP transfer:

1. **Web Transfer:**

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to transfer DICOM images and other required files to the ICL through website upload.imagingcorelab.com. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

2. **FTP Transfer:**

Any FTP software can be used to initiate access to the secure FTP Server of the ICL. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

Send an e-mail notification to inform the Imaging Core Lab at the specific trial email of the data submission **once the data transfer is completed**.

3. **Shipment/Mail (not preferred but accepted):**

If the above electronic data transfers cannot be achieved, the de-identified images in DICOM format can be burned to a CD, labeled with info of patient ID, study date, baseline/follow-ups on the CD cover, and mailed to the ICL at:

[redacted]
Phone: [redacted]
Fax: [redacted]

Any questions or problems about the data transfer to the Imaging Core Lab, email the ICL at the specific trial email [redacted], or call the ICL IT group at [redacted] or [redacted] for help.

9.1.2 Safety and Tolerability Assessments

Hematology and chemistry assessments (WBC, ANC, Hgb, PLT, SGOT AST, total bilirubin, alkaline phosphatase, creatinine, potassium, sodium albumin) and LDH/Uric acid levels will be reviewed at screening and monitored throughout the study. Patients will visit the clinic monthly for laboratory assessments, physical examination, concomitant medication review, and adverse event assessment. Refer to the study table assessment table in Section 9 for details on study assessments and procedures performed for this trial.

9.1.3 Electrocardiogram

ECG will be performed at screening and at end of study treatment. As there are rare events of arrhythmia/afibrillation associated with ibrutinib, ECGs may also be performed during the course of the study as deemed needed by the investigator.

9.1.4 Biomarkers/Correlative Studies

Bone marrow aspirates will be collected at pre-treatment and end of cycle 1 MicroRNA-profiling.

Peripheral blood will be collected at pretreatment and after cycles 1, 3, and 6 for immunome studies. Refer to Section 13 for detailed correlative studies information.

9.1.5 Follow-up for Other Malignancies

Occurrences of any new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported throughout study participation, including duration of study treatment and during any protocol specified follow-up periods.

Table 15 Schedule of Assessment

Treatment Day → Assessments and Procedures ↓	≤ 14 days prior to registration	Day 1 (all cycles)	Day 15 ± 2 days (all cycles)	End of Cycle 1	End of Cycle 3	End of Cycle 6	At end of treatment or treatment discontinuation
History and exam, weight[a]	X	X	X				X
Height	X						
ECOG Performance Status	X	X	X				X
Adverse event assessment	X	X	X				X
Concomitant Medications	X						X
Hematology group: WBC, ANC, ALC, Hgb, and PLT[b]	X	X	X				X
Chemistry group SGOT AST, total bili, Alk Phos, Creatinine, potassium, calcium, magnesium, phosphorus, sodium, albumin), blood glucose[b]	X	X	X				X
TSH, Free T4[cc]	X						
LDH, Uric Acid[b]	X	X	X				X
Serum pregnancy test[d]	X						
Complete body CT	X	X[e]				X[e]	X[e]
Bone Marrow Biopsy[f]	X			X			
Mandatory blood specimens[g]	X	X[g]		X[g]	X[g]	X[g]	
ECG[h]	X						X

Treatment Day → Assessments and Procedures ↓	≤ 14 days prior to registration	Day 1 (all cycles)	Day 15 ± 2 days (all cycles)	End of Cycle 1	End of Cycle 3	End of Cycle 6	At end of treatment or treatment discontinuation
Serum Immunoglobulins, monoclonal protein and free light chain; beta 2 microglobulin[i]	X						X

a. History, exam, and weigh will be done on day 1 of subsequent cycles after cycle 2
b. Labs will be done weekly for the first 2 cycles, then on day 1 of subsequent cycles
c. TSH and Free T4 at screening and every 2 cycles
d. To be performed within 7 days of receiving drug.
e. If clinically indicated for those with extramedullary disease indicated on baseline CT at completion of cycle 6 (cycle 6 day 28 ±3 days) or to confirm CR
f. 2 tubes of 5 ml each of bone marrow aspirates in green tube (2) to be collected pre-treatment (prior to start of cycle 1) and at end of cycle 1 (prior to start of cycle 2).
g. 15 ml peripheral blood to be collected prior to start of treatment and at end of cycles 1, 3, and 6 for the immunome correlate
h. ECG should be performed within 14 days prior to registration and end of treatment, and as needed during the course of the study.
i. Immunoglobulins, serum free light chains (kappa and Lambda), serum monoclonal protein, beta 2 microglobulin ≤ 14 days prior to registration and day 1 of each cycle. 24-hour Urine Protein and immunofixation ≤ 14 days prior to registration, and every 3 months.

10. Adverse Events

10.1. Definitions

10.1.1 Adverse Events

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

10.1.2 Serious Adverse Events

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.1.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

- An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of an SAE/Reaction
- Qualifies for expedited IND safety reporting to the FDA, Competent Authorities and other regulatory bodies by meeting all three definitions of suspected adverse reaction, serious, and unexpected.
- Expected adverse reactions and related serious adverse reactions to study drugs are listed in the IB/package insert(s). A serious adverse reaction that is not included in the IB/package insert(s) should be evaluated and reporting on the study specific SAE form by the site investigator as a SUSAR within 24 hours after learning of the event.

10.1.4 Events of Clinical Interest

Adverse Events of special interest are events that the drug manufacturer or the Sponsor of the study, AFT, are actively monitoring as a result of a previously identified signal (even if non-serious).

10.2. Expected Adverse Events

Expected toxicities for ibrutinib combination therapy are summarized above in Section 1.4.1.2.

For more detailed information refer to the current version of the IB.

10.3. Adverse Events of Special Interest (AESIs)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to AFT into the Rave EDC system within 24 hours of becoming aware of the event(s). AFT will also report to Pharmacyclics Drug Safety, or designee, on the Serious Adverse Event Report Form via email or fax within the 15 days of awareness.

10.3.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

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

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v 5.0.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.5.4.

10.4. Adverse Event Reporting Exceptions

The following are NOT considered AEs:

- **Disease progression:** The term disease progression should not be reported as an adverse event term. As an example, “worsening of underlying disease” or the clinical diagnosis that is associated with disease progression should be reported.
- **Baseline condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

  Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should be reported via routine reporting methods in the Rave data

capture system. Deaths occurring within the reporting window, even if considered to be related to disease progression as the cause of death should be reported as a Serious Adverse Event with death noted as the outcome of the event.

- **Asymptomatic Treatment-related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures

10.5. Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical study are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. All AEs whether serious or non-serious, will be captured from the time of first study related procedure until 30 days following cessation of treatment. Any increase of a documented baseline condition from screening/history will be reported as an adverse event. Adverse events are entered into the eCRF in Rave Electronic Data Capture (EDC) system.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

10.5.1 Serious Adverse Event Reporting

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

All serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, through 90 days following cessation of treatment, whether or not related to the investigational product, require reporting into Rave EDC within 24 hours of awareness of the event.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

NOTE: Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should be reported via routine reporting methods in the Rave EDC system. Deaths occurring within the reporting window, even if considered to be related to disease progression as the cause of death should be reported within Rave EDC system with death noted as the outcome of the event.

10.5.2 Pregnancy Reporting

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

A female subject or female partner of a male subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug Any female subjects receiving study drug(s) who become pregnant must immediately discontinue

study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a female subject or female partner of a male subject must be reported from the time of first dose to 90 days after the last dose of study drug must be reported.

All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. In pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old. Pregnancies should be reported to AFT as serious in the Rave EDC system on the pregnancy form within 24 hours of becoming aware of the event(s). AFT will submit SAE pregnancy reports to Pharmacyclics per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

10.5.3 Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival. If observed, enter data in the corresponding eCRF in Rave EDC.

10.5.4 Adverse Events of Special Interest (AESI)

Adverse events of Special Interest (AESI) will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to AFT into the Rave EDC system within 24 hours of becoming aware of the event(s). AFT will report to Pharmacyclics per SAE reporting timelines.

10.5.5 Expedited Reporting for Serious Adverse Events and AESIs

All serious adverse events and AESIs (initial and follow-up information) will be reported to AFT in the Rave EDC system within 24 hours of becoming aware of the event(s). AFT will report to Pharmacyclics per regulatory reporting timelines. AFT may request follow-up and other additional information from the Investigator.

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

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

Expedited AE reporting timelines are defined as:

- "All Grade 3, 4 and 5 AEs: 24-Hour; 4 Calendar Days" – The AE must initially be reported via Rave EDC System ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 4 calendar days of the initial 24-hour report.
- "All Grade 1 and 2 AEs resulting in hospitalization or prolonged hospitalization: 24-Hour; 10 Calendar Days" – The AE must initially be reported via Rave EDC System ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 10 calendar days of the initial 24-hour report.

10.5.6 Special Reporting Situations

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

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

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an AE, it should be recorded on the AEs eCRF. If the AE is considered serious, it should be recorded on the AEs eCRF as serious within Rave EDC. The serious adverse event should also be reported on the Serious Adverse Event Report Form which should be sent via email or fax to Pharmacyclics Drug Safety or designee within 15 calendar days.

10.6. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and entered into the eCRF in Medidata® Rave Electronic Data Capture (EDC) system (Rave EDC).

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

10.6.1 Assessment of Severity of Adverse Events

Definitions found in the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v 5.0) will be used for grading the severity (intensity) of non-hematologic AEs. The CTCAE v5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each

referenced AE. Should a subject experience any AE not listed in the CTCAE v5.0, the following grading system should be used to assess severity:

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to AFT (or designee) using the same procedure used for transmitting the initial SAE report.

10.6.2 Assessment of Causality of Adverse Events

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

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

10.7. Expedited Safety Reporting to Regulatory Agencies and Pharmacyclics

Suspected Unexpected Serious Adverse Reaction (SUSAR)

- An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of an SAE/Reaction
- Qualifies for expedited IND safety reporting to the FDA, Competent Authorities and other regulatory bodies by meeting all three definitions of suspected adverse reaction, serious, and unexpected.
- Expected adverse reactions and related serious adverse reactions to study drugs are listed in the IB/package insert(s). A serious adverse reaction that is not included in the IB/package insert(s) should be evaluated and reporting on the study specific SAE form by the site investigator as a SUSAR within 24 hours after learning of the event.

The Safety Management group at AFT will complete and submit expedited regulatory safety reports (MedWatch, CIOMS, etc.) of SUSARs to the relevant regulatory/competent authorities within the required reporting timelines. In general, AFT is required to report all non-fatal or non-life threatening SUSARs to the FDA within 15 calendar days of investigator awareness of the event and all SUSARs resulting in hospitalization, prolongation of hospitalization, or death within 7 calendar days of AFT awareness. AFT will submit safety reports to Pharmacyclics in parallel to regulatory agency submission and no later than 15 calendar days from AFT's first awareness date.

11. Drug Information

11.1. Ibrutinib

Ibrutinib is an inhibitor of Brutin's tyrosine kinase (BTK) with the empirical formula C25H24N6O2 and a molecular weight of 440.50 Daltons. Ibrutinib is also known as IMBRUVICA and is distributed and manufactured by several manufacturers.

11.1.1 Form

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

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

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

11.1.2 Storage and Stability

Bottles of ibrutinib should be stored at room temperature 20°C to 25°C (68°F to 77°F). Excursions are permitted between 15°C and 30°C (59°F to 86°F). Capsules should be retained in original package until dispensing.

11.1.3 Handling

Bottles of ibrutinib should be stored in conditions specified in Section 11.1.2 above, per package insert, or according to institutional standards.

11.1.4 Availability

Ibrutinib is not approved for this indication and will be supplied free of charge by Pharmacyclics LLC.

11.1.5 Preparation

A supply sufficient for one cycle (28 days) will be provided to the patient at the beginning of each cycle.

11.1.6 Administration

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

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up the missed dose. The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis.

11.1.7 Ordering

Initial and re-supply of ibrutinib should be requested using the PCYC drug order system. Additional instructions will be provided to sites under separate cover.

11.1.8 Accountability

Site investigators or designated responsible parties must maintain a record of the inventory of distribution of ibrutinib using the appropriate documentation method (e.g. drug accountability log).

The investigator is responsible for keeping accurate records of the clinical supplies received from AFT or designee, the amount dispensed to patients and the amount remaining at the conclusion of the study.

11.1.9 Destruction and Return

Sites may destroy unused study drug according to their institutional policies. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty containers (if applicable) and unused investigational product to the clinic site.

11.2. Lenalidomide (REVLIMID®)

11.2.1 Description

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2H-isoindol-2-yl) piperidine-2,6-dione. The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

11.2.2 Form

Lenalidomide is off-white to pale-yellow solid powder. Lenalidomide is soluble in organic solvent/water mixtures and buffered aqueous solvents. It is more soluble in organic solvents and low pH solutions.

Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml.

Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

11.2.3 Storage and Stability

Lenalidomide is commercially available and will be dispensed by a pharmacist registered in the Revlimid REMS® program. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

11.2.4 Handling

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

11.2.5 Availability

Lenalidomide is commercially available and will be dispensed by a pharmacist registered in the Revlimid REMS® program.

11.2.6 Ordering

Lenalidomide will be provided as commercial supply in accordance with the Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS® program. Prescriptions must be filled within 14 days, unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

11.2.7 Accountability

Lenalidomide is commercially available therefore, no drug accountability records are required. The investigator is responsible for monitoring patient compliance by monitoring patient diary and or pill count.

11.2.61 Destruction and

Participants will be instructed to return empty bottles or unused capsules via the Revlimid REMS® program.

11.3. Dexamethasone

11.3.1 Description

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17, 21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water. The empirical formula is C22H29FO5

11.3.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 4 mg tablets for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

11.3.3 Storage and Stability

At the study site, all study drugs will be stored in a locked, safe area to prevent unauthorized access.

Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements.

11.3.4 Handling

Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

11.3.5 Availability

Dexamethasone supply will be obtained through commercial supply.

11.3.6 Preparation

Dexamethasone is an oral drug and does not require specific preparation details.

11.3.7 Ordering

The investigator or designee will order drug supply from commercial supply.

11.3.8 Accountability

The investigator is responsible for keeping accurate records of the clinical supplies received from AFT or designee, the amount dispensed to patients and the amount remaining at the conclusion of the study.

11.3.62 Destruction and

Sites may destroy unused study drug according to their institutional policies. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty containers (if applicable) and unused investigational product to the clinic site.

12. Data Collection and Management/ Data and Specimen Submission

12.1. Data Collection and Submission

Data collection for this study will be done through the Medidata® Rave clinical data management system. Access to the study in Rave EDC is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System. See Data Entry Guidelines for additional instructions.

12.2. Specimen Collection and Submission

Bone marrow aspirates will be collected at a pre-treatment and end of cycle 1 correlatives. Two 2 ml tubes will be collected at each time point.

Peripheral blood will be collected at pretreatment and after cycles 1, 3, and 6 for immunome studies. 15 ml of blood will be collected at each time point.

Table 16 Research Blood and Body Fluid to be Collected

Correlative Study (Section 13 for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	After registration, prior to start of treatment	At completion of Cycle 1, 3, and 6
immunome studies	Mandatory	Peripheral blood	X	X
	Mandatory	Peripheral blood	X	X
bone marrow aspirates	mandatory	Bone marrow fluid	X	X*

*at the end of Cycle 1 only

Details for processing and shipping of specimens can be found in the study specific correlative science manual.

13. Correlative Studies

To be performed in [redacted]

13.1. Peripheral Blood and Bone Marrow Samples

Peripheral blood samples and bone marrow samples will be sent to the Alliance Foundation Biorepository, who will process the samples before sending them to City of Hope. Peripheral blood and bone marrow aspirates will be used to analyze Th1/Th2 response in treated patients and the bone marrow aspirates will be used to isolate CD-138+ myeloma cells for the analysis of Btk, microRNA (miR) and mRNA expression for correlation with outcomes.

13.2. Immunome

The immunome correlative will be completed in the expansion phase only. Peripheral blood will be collected at pre-treatment, after cycles 1, 3, and 6, and the PBMC fraction will be used to quantify immune subset changes over the course of treatment including B cells, cytotoxic T cells, T regulatory cells, T central memory cells, NK cells, NKT cells, and B-cell subsets by flow cytometry to assess for any changes that may correlate with outcome. Specifically, 5x106 PBMC will be stained using Maxpar® Direct™ Immune Profiling System and detect by mass cytometry analysis. We are planning to collect at least 40 longitudinal samples for the analysis.

At Pre-treatment and end of cycle 1 (before start of cycle 2) bone marrow aspirates will be collected for total RNA sequencing. Specifically, CD138+ plasma cells will be purified from total marrow cells of patients by Human Whole Blood CD138+ Selection Kit (Cat#18387, Stem Cell Technologies), as described in section 13.3. We are planning to perform RNA sequencing in total 10 longitudinal samples isolated from 5 patients.

13.3. Immunohistochemistry analysis (IHC) in bone marrow biopsies

Bone marrow core biopsies collected at the same time of the bone marrow aspirates (Pre-treatment and end of cycle 1) will be used to perform IHC staining to determine levels of B-cell receptor signaling and Btk activation in the bone marrow of the myeloma patients after treatment. Phosphorylated and total Btk, phosphorylated and total PLCγ and phosphorylated and total ERK will be assessed by IHC and coexpression with CD-138+ MM cells will be also assessed. Furthermore, by RT-PCR we will evaluate the variation in BTK mRNA levels associated to the treatment as previously described.

13.4. Measurement of Effect

Patients enrolled onto this trial must have measurable disease defined as disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of FLC and is defined by at least one of the following three measurements:

- Serum M-protein > (0.5 g/dl) g/dl
- Urine M-protein > 200 mg/24 h
- Serum FLC assay: Involved FLC level > 10 mg/dl (> 100 mg/l) provided serum FLC ratio is abnormal.

The disease response will be assessed using criteria based on the International Working Group Uniform Response Criteria in Section 15.3.1. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by FreeLite™ Disease Response Criteria provided in Section 15.3.2.

The same method of assessment and technique should be used for disease measurement

throughout the study. Disease response should be confirmed by two consecutive assessments at a minimum of 6 weeks apart.

13.5. Methods for Evaluation of Measurable Disease

All baseline evaluations should be performed on Cycle 1, Day 1 of therapy. Response will be assessed by M-protein quantification, protein electrophoresis and immunofixation from serum, a 24-hour urine collection and serum free light chain. In addition, bone marrow aspiration and biopsy will be performed confirm CR and differentiate between CR and stringent CR.

13.6. Response Criteria

13.6.1 International Myeloma Working Group Response Criteria

Table 17

Response	*IMWG criteria*
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow. In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
Stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease

Progressive disease	Increase of ≥ 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

Additional response criteria for specific disease states

Minor response in patients with relapsed and refractory myeloma adapted from the EMBT Criteria ≥ 25% but < 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response).

13.6.2 FreeLite™ Disease Response Criteria

Table 18

Response	*FreeLite™ criteria*
CR	For those patients being followed by serum free light chain (and NO measurable serum or urine M-spike), which were immunofixation negative at enrollment, normalization of serum free light chain ratio. Normalization is defined as the serum free light chain ratio being within the normal range. If the serum free light chain ratio is not within the normal range, but the individual kappa and lambda light chain values are within normal range, this may be considered CR.
PR	If only measurable parameter is serum immunoglobulins free light chain (FLC), EITHER of the following changes quality as partial response: - A 50% decrease in the difference between involved and uninvolved FLC levels; OR - A 50% decrease in the level of involved FLC AND a 50% decrease (or normalization) in the ratio of involved/uninvolved FLC
Progressive Disease	If only measurable parameter is serum immunoglobulins free light (FLC), either of the following qualify as progression: - 50% increase in the difference between involved and uninvolved FLC levels from the lowest response level, which must also be an absolute increase of at least 10 mg/dL; OR - 50% increase in the level of involved FLC AND a 50% increase in the ratio of involved/uninvolved FLC from the lowest response level.

14. Statistical Considerations

14.1. Overview of the Study Design

This is a single-arm, open label, phase Ib study of Ibrutinib in combination with lenalidomide and dexamethasone in adult (age 18 years and older) patients with relapsed/refractory MM. A 3+3 phase I clinical trial design as described in Section 6.0 was chosen to determine the MTD of Ibrutinib in combination with lenalidomide given on days 1-21 of a 28-day cycle and dexamethasone given orally weekly. An expansion cohort of 10 patients will be treated at the MTD to gather additional safety and anti-tumor activity data.

As of April 15, 2021, 2 patients have been enrolled onto dose level 2.

- If none of the first 3 patients treated at dose level 2 develops a DLT, then the next cohort of 3 patients will be enrolled onto dose level 3 and biospecimen collection will begin for all subsequent patients enrolled.
- If one of the 3 patients treated at dose level 2 develops a DLT, then the next cohort of 3 patients will be enrolled at dose level 2 and correlatives biospecimens will be collected from these patients.
    - If 2 or more of the 6 patients treated at dose level 2 develops a DLT then an additional 10 patients will be enrolled onto dose level 1 so that a total of 10 patients will have provided biospecimens at the MTD. (Note: Total sample size will be 6 [from dose level 1] + 6 [from dose level 2] + 10 [for dose expansion] = 22. Biospecimens will be available for 10 patients treated at the MTD.)
- If 2 or more of 3 patients treated at dose level 2 has an DLT, an additional 10 patients will be enrolled onto dose level 1 to further assess safety and collect specimens for correlative aims. (Note: Total sample size will be 6 [from dose level 1] + 3 [from dose level 2] + 10 [for dose expansion] = 19. Biospecimens will be available for 10 patients treated at the MTD.)
- If at most 1 of 6 patients treated at dose level 2 develops a DLT and 2 or more of the 3-6 patients treated at dose level 3 develops a DLT, then an additional 7 patients will be enrolled onto dose level 2 so that a total of 10 patients will have provided biospecimens at the MTD. (Note: Total sample size will be 6 [from dose level 1] + 6 [from dose level 2] + 6 [maximum number anticipated on dose level 3] + 7 [for dose expansion] = 25. Biospecimens will be available for 10 patients treated at the MTD.)
- If at most 1 of 6 patients treated at dose level 2 develops a DLT and 1 or fewer of the 6 patients treated at dose level 3 develops a DLT, then an additional 4 patients will be onto dose level 3 so that a total of 10 patients will have provided biospecimens at the MTD. (Note: Total sample size will be 6 [from dose level 1] + 6 [from dose level 2] + 6 [maximum number anticipated on dose level 3 to establish it as MTD] + 4 [for dose expansion] = 22. Biospecimens will be available for 10 patients treated at the MTD.)
- If at most 1 of 6 patients treated at dose level 3 develops a DLT then an additional 4 patients will be enrolled onto dose level 3 so that a total of 10 patients will have provided biospecimens at the MTD. (Note: Total sample size will be 6 [from dose level 1] + 3

[from dose level 2] + 6 [maximum number anticipated on dose level 3] + 4 [for dose expansion] = 19. Biospecimens will be available for 10 patients treated at the MTD.)

- If 2 or more of the 3-6 patients treated at dose level 3 develops a DLT then an additional 7 patients will be enrolled onto dose level 2 so that a total of 10 patients will have provided biospecimens at the MTD. (Note: Total sample size will be 6 [from dose level 1] + 3 [from dose level 2] + 6 [maximum number anticipated on dose level 3] + 7 [for dose expansion] = 22. Biospecimens will be available for 10 patients treated at the MTD.)

14.2. Sample Size, Accrual Time and Study Duration

A minimum of 6 and a maximum of 25 patients will be accrued. We anticipate that 3 patients will be enrolled and followed for the development of a DLT every 4-6 months, the time between determination of MTD and opening of the expansion cohort to be 2 months, and 1 patient per month would be enrolled during the expansion phase of the study. Thus, the enrollment period would be approximately 42 to 48 months.

14.3. Definitions of Endpoints and Analysis Plan

14.3.1 Patient Evaluability

All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be included in the analysis of the safety and clinical outcome data.

14.3.2 Statement for Primary Endpoint

The primary endpoint of the dose escalation portion of this phase I study is the MTD. The maximum tolerated dose is defined as the highest dose level among those tested where at most one out of 6 patients develops a DLT prior to the start of their second cycle of treatment and the next highest dose level is such that 2 or more patients among the maximum of 6 patients treated at that dose level developed a DLT prior to the start of their second cycle of treatment.

The primary endpoint of the expansion portion of this phase I study is the objective response rate. The objective response rate is the percent of patients who meet the International Myeloma Working Group Response Criteria for sCR, CR, VGPR, or PR on two consecutive evaluations at least 4 weeks apart among the patients who began study treatment. A 90% binomial confidence interval will be constructed for the overall objective response rate.

14.3.1 Statement for Secondary Endpoints

Secondary Endpoints include:

Maximum Toxicity Grade:

The maximum grade of each type of toxicity will be recorded for each patient. For each toxicity reported by dose level, the percentage of patients developing any degree of that toxicity as well as the percentage of patients developing a severe degree (Grade 3 or higher) will be determined.

Number/Duration of Response:

For each dose level, the number of response and the duration of response will be tabulated. The duration of response is the time from initiation of first response to first documentation of disease

progression or death. Patients who have not progressed will be censored at the date of their last disease evaluation.

Progression-free Survival (PFS)/ Overall Survival (OS)

Secondary endpoints for the expansion cohort include progression-free survival (PFS) and overall survival (OS) time.

Survival time is defined as the time from study entry to death due to any cause.

Progression-free survival time is the time from study entry to the documentation of disease progression or death due to any cause.

If a patient dies without a recurrence documented, the patient will be censored at the date of last disease evaluation. The distribution of response times, progression-free survival times and survival times will be estimated using the Kaplan-Meier method.

14.4. Data and Safety Monitoring

Interim reports from the statistical team will be generated for the Data and Safety Monitoring Board (DSMB).

15. General Regulatory Considerations and Administrative Procedures

15.1. Compliance with Study Enrollment and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

15.2. Regulatory and Ethical Compliance

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual.
Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

15.3. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of

the patient (i.e. would not be indicated outside the study). The proposed Informed Consent Form and consenting process must comply with the GCP guidelines, regulatory requirements and be consistent with IRB/institutional policies.

15.4. Responsibilities of the Investigator/IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312 (21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Responsibilities (Form FDA 1572) and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The Investigator is responsible for the overall study compliance, execution, oversight and management of the study at their site, and satellites if applicable.

As specified in 21CFR 312.62(Investigator Record Keeping and Record Retention) and ICH E6 Sections 4.9 and 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, protocol documents, Institutional Review Board (IRB) approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete electronic case report forms (eCRFs) in a timely manner.

15.5. Financial Disclosures

Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

15.6. Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff. AFT does not provide waivers for protocol deviations.

15.7. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to

implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated. Because administrative processing of amendments may take time which could impact study conduct, AFT may release operational memos to allow such changes to the protocol conduct to occur prior to the formal amendment review without being considered a protocol deviation. This is particularly true for changes which impact patient safety. Such memos should be processed per local IRB/institutional standard.

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB as per institutional guidelines.

15.8. Retention of Records (Study Documentation, record keeping, and retention of records)

Any records and documents relating to the conduct of this study and the distribution of investigational product, must be retained by the investigator until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself.

15.9. Data Confidentiality

Patient medical information both, associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on individual patients will in generally not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

Data collected during this study may be used to support the development, registration or marketing of an investigational product. All data collected during the study will be controlled by the sponsor, AFT. AFT will abide by all relevant data protection laws. After a patient has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the sponsor and the manufacturer to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may be additionally reviewed by auditors or by regulatory authorities.

15.10. Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

Medidata® Rave electronic data capture (EDC) system will be used for this study. The study data will be entered by study-site personnel from the source documents onto an eCRF in Rave EDC. eCRFs will be completed in a timely manner.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs. At study completion, when the database has been declared to be complete and accurate, the database will be locked.

15.11. Site Monitoring

Monitoring visits will be conducted by representatives of the Alliance Foundation according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6).

15.12. Data and Safety Monitoring Board (DSMB)

The Alliance Foundation Trials Data Safety Monitoring Board will be monitoring this study to ensure objectivity and the safety of participants. The DSMB will meet twice a year either at a face-to-face meeting or by teleconference. At each meeting, the study will be reviewed for safety and progress toward completion.

15.13. Regulatory Reporting

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, AFT's guidelines, and Institutional Review Board (IRB) policy.

15.14. Audits and Inspections

To enable evaluations and/or audits from health authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). In the event that the investigator or other site personnel are notified of a Health Authority's intent to inspect the site(s), notification will be sent to [redacted] immediately upon awareness.

15.15. Early Discontinuation of the Study

Early study termination will be the result of the criteria specified below:

- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

- Plans to modify or discontinue the development of the study drug

15.16. Publication of study protocol and results

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this trial. No investigator may present or publish any portion of this study without written approval from AFT.

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Appendices

Appendix I: ECOG Performance Status

Appendix II: Inhibitors and Inducers of CYP3A

Appendix III: Child-Pugh score

Appendix I: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

Appendix II: Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx. The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 5.4 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	**Inducers of CYP3A**
Strong inhibitors:	Carbamazepine
indinavir	Efavirenz
nelfinavir	Nevirapine
ritonavir	Barbiturates
clarithromycin	Glucocorticoids
itraconazole	Modafinil
ketoconazole	Oxcarbarzepine
nefazodone	Phenobarbital
saquinavir	Phenytoin
suboxone	Pioglitazone
telithromycin	Rifabutin
cobicistat	Rifampin
boceprevir	St. John's Wort
mibefradil	Troglitazone
telaprevir	
troleandomycin	
posaconazole	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir/ritonavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole	
imatinib	
Weak inhibitors:	

cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

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

Appendix III: Child-Pugh Score

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

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

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . "Transection of te oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.