NCI Protocol #: *N/a*

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BMS Protocol #: *CA180-703*

TITLE: Dasatinib in patients with Waldenström Macroglobulinemia (WM) progressing on Ibrutinib

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Agent(s): *Dasatinib*

IND: 143803
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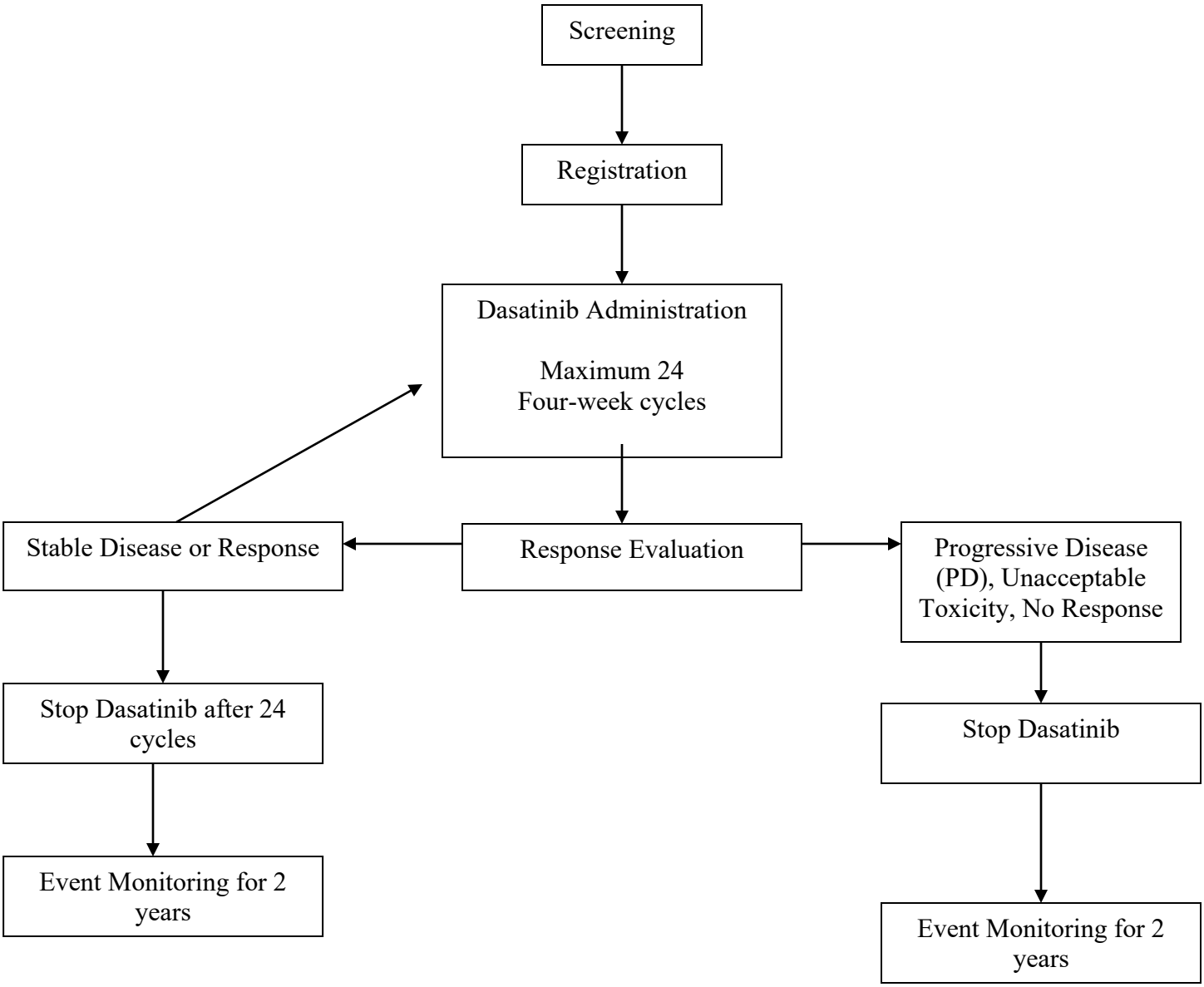
SCHEMA


Screening
Registration
Dasatinib Administration
Maximum 24
Four-week cycles
Response Evaluation
Stable Disease or Response
Progressive Disease (PD), Unacceptable Toxicity, No Response
Stop Dasatinib after 24 cycles
Event Monitoring for 2 years
Stop Dasatinib
Event Monitoring for 2 years

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1. OBJECTIVES

1.1 Study Design

This is a Phase I Pilot, single center study designed to explore the safety of dasatinib, a pleiotropic kinase inhibitor that non-covalently blocks HCK and BTK, both downstream mediators of survival signaling in MYD88 mutated WM patients (Yang et al, 2013; 2016). The study will examine the safety of dasatinib, a non-covalent inhibitor of BTK and HCK in symptomatic MYD88 mutated WM participants who are progressing on the covalent BTK-inhibitor ibrutinib, an FDA approved treatment for symptomatic WM. Unlike ibrutinib that binds to BTK Cys 481, a frequent site of acquired resistance in WM (Xu et al, 2017), dasatinib binds at BTK Thr 474 (Hantschel et al, PNAS 2007). Dasatinib is FDA approved for Chronic Myelogenous Leukemia (CML), and we plan to use the FDA approved dose (100mg PO QD) in this study. Treatment will be comprised of dasatinib administered orally starting day 1 of cycle 1 for up to 24 cycles.

At the Screening visit, a medical history will be obtained and a complete physical examination will be performed including vital signs and an ECOG performance status. Bone marrow biopsy and aspirate and CT scanning of the chest, abdomen, and pelvis must be performed within 90 days prior to Cycle 1 Day 1. Clinical laboratory tests are required per section 10 Study Calendar.

Participants who meet the eligibility requirements will be enrolled on study and initiated on study drug. Participants will be seen in clinic and have routine laboratory studies prior to each cycle of dasatinib for the first 3 cycles and every 3 cycles there after until study completion. Participants will be evaluated for tolerance and response at each visit for the duration of the trial. The participants will be followed for 2 additional years after completion of study drug. Participants will be eligible to continue on therapy for up to 2 years as long as they do not have unacceptable toxicity or demonstrate progressive disease. Response criteria updated at the Sixth International Workshop on Waldenström's macroglobulinemia (Owen et al, BJH 2013) will be used to assess response, stable disease, and progressive disease. Response outcomes to be determined will include: ORR and major response rates (including VGPR and CR rates); median PFS and TTNT.

1.2 Primary Objectives

- To evaluate the toxicity profile of dasatinib in WM patients who progressed on ibrutinib

1.3 Secondary Objectives

- To evaluate the ORR of dasatinib in WM patients who are progressed on ibrutinib.
- To evaluate the rate of CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) and progressive disease (PD) to dasatinib in WM patients who progressed on ibrutinib.
- To evaluate progression-free survival, time to next therapy (TTNT), and overall survival to dasatinib in WM patients who progressed on ibrutinib.
- To evaluate the impact of MYD88 and CXCR4 mutations on response to dasatinib in WM patients who progressed on ibrutinib.

2. BACKGROUND

2.1 Study Disease(s)

WM is a rare B-cell lymphoproliferative disorder characterized by the uncontrolled accumulation of IgM-producing lymphoplasmacytic cells (Swerdlow et al, 2008) Such malignant cells accumulate in the bone marrow, liver, spleen and lymph nodes. WM is diagnosed by the presence of lymphoplasmacytic cells in the bone marrow and an IgM monoclonal spike (M-spike) identified in a serum protein electrophoresis (SPEP). The incidence of WM in the United States (US) is approximately 3 per million persons per year accounting for 1500 new cases per year (Sekhar et al, 2012). The clinical course of WM is variable and although patients might experience an overall survival (OS) measured in decades(Castillo et al, 2014; 2015), WM remains incurable with current therapeutic regimens. Hence, the disease course is characterized by continual relapses, each harder to treat than the previous one. Additionally, many of the disabling symptoms associated with the disease, such as hyperviscosity, fatigue, anemia or neuropathy, can be exacerbated by our therapy (Treon et al, 2015a). Hence, the careful evaluation of agents with novel mechanisms of action is needed to improve the quality of life (QOL), and response and survival rates in patients with WM.

Previously, our group identified a recurrent mutation in the MYD88 gene (MYD88 L265P), which is seen in over 90% of cases with WM (Treon et al, 2012). The occurrence of this mutation in WM has since been validated in several independent cohorts (Jimenez et al, 2013; Mori et al, 2013; Poulain et al, 2013; Varettoni et al, 2013). . In contrast, the MYD88 L265P gene mutation was not detected in patients with IgM myeloma and was detected in less than 10% of patients with marginal zone lymphoma. The high specificity and sensitivity of the MYD88 L265P gene mutation has obvious diagnostic implications in patients in whom a diagnosis of WM is suspected but uncertain. The MYD88 L265P gene mutation has shown to support growth and survival of WM cells in several studies. A knockdown model of MYD88 showed decreased survival of MYD88 L265P expressing WM cells, whereas survival was more enhanced by knock-in of mutant *versus* wild-type MYD88 (Yang et al, 2013). MYD88 acts as an adaptor molecule in toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling Waters et al, 2007). Following stimulation of TLR or IL-1R, MYD88 is recruited to the activated receptor complex as a homodimer which complexes with IL-1R-associated kinase 4 (IRAK4) and subsequently activates IRAK1 and IRAK2 (Lin et al, 2010). IRAK1 activation then leads to NF-κB activation via IκBα phosphorylation (Kawagoe et al, 2008). Previously, our study showed that MYD88 L265P triggered the Bruton's Tyrosine Kinase (BTK) pathway (Yang et al, 2013). In this pre-clinical study, the activation of BTK by MYD88 could be abrogated by the use of the covalent BTK kinase inhibitor ibrutinib that binds BTK at Cys481 .

We subsequently reported the occurrence of recurrent somatic CXCR4 gene mutations in approximately 30-40% of WM patients (Hunter et al, 2014). The somatic mutations occur in the C-terminal domain,and are similar to those observed in patients with WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome. These mutations regulate signaling of CXCR4 by its ligand SDF-1a In WM patients, two classes of CXCR4 mutations occur: non-sense ($CXCR4^{WHIM/NS}$) and frameshift ($CXCR4^{WHIM/FS}$) mutations (Hunter et al, 2014; Treon et al, 2014) Non-sense and frameshift mutations are almost equally divided among WM patients, and over 30 different types of CXCR4 mutations have been identified. Preclinical

studies with the most common CXCR4 S338X mutation in WM have shown sustained signaling of AKT, ERK and BTK following SDF-1a binding in comparison with wild-type CXCR4, as well increased cell growth and survival of WM cells (Cao et al, 2014; Rocarro et al, 2014)

In early 2015, following a prospective study led by our group, the U.S. FDA and the EMA approved the use of the oral BTK ibrutinib for the treatment of patients with symptomatic WM. The approval was based on the results of a phase II study in 63 patients with relapsed and/or refractory WM, in which ibrutinib induced an overall response rate (ORR) of 91% and a major response rate of 77%, as well as 5-year progression-free (PFS) and overall survival (OS) of 54% and 87%, respectively (Treon et al, 2020). Despite these exceptional results and the ease of administration, ibrutinib therapy is associated with toxicity, and response rates are affected by the MYD88/CXCR4 mutational status. Among other minor adverse events, ibrutinib therapy has been associated with an increased risk of bleeding with procedures prompting temporary hold of ibrutinib to minimize risk. Also, atrial fibrillation can occur on ibrutinib therapy in up to 10% of patients with WM. WM patients who carry MYD88 and CXCR4 mutations experience lower rates of ORR and major response rates than patients with MYD88 only disease. WM patients who are wild type for MYD88 and CXCR4, the no major response rates were observed.

Progression on ibrutinib has been observed in patients with WM, and it has been associated with the development of mutations in BTK, including BTK C481S mutation, those downstream of BTK such as PLCG2 mutations, and more recently through whole exome sequencing 6q and 8p deletions encompassing regulators of BTK, MYD88/NFKB, and apoptosis. (Xu et al, 2017; Cen et al, 2018; Jimenez et al, 2020).WM patients who become resistant to ibrutinib experienced difficult-to-control disease progression and has been associated with an increased risk of death (Gustine et al, 2018).

Therefore, there is an unmet need for highly effective, well-tolerated therapies in WM patients who are progressing on ibrutinib that would be indifferent to the genomic profile of WM patients.

2.2 IND Agent Dasatinib

Dasatinib (BMS-354825) is a potent, broad-inhibitor of 5 critical oncogenic tyrosine kinases/kinase families (BCR-ABL, SRC, c-KIT, PDGF receptor β [PDGFRβ], and ephrin [EPH] receptor kinases), each of which is linked to multiple forms of human malignancies and was discovered and developed by BMS. Overexpression or activation of these kinases plays a critical role in the etiology of various cancer types, as well as in the malignant behavior associated with these diseases, such as unregulated proliferation and metastasis. Dasatinib is approved in the United States (US), Europe (EU), and several other countries for the treatment of adults in all phases of chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy including imatinib, and Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to prior therapy. In a randomized trial, dasatinib at a dose of 100 mg PO QD showed to be more effective than imatinib 400 mg PO QD on inducing responses in patients with chronic phase CML. Therapy continued to disease progression or unacceptable toxicity. With regard to safety, grade 3 or 4 neutropenia, thrombocytopenia and anemia were seen in 21%, 19% and 10% of CML patients. Most of the adverse events were grade 1 or 2 and included anemia (90%), thrombocytopenia (70%), neutropenia (65%), fluid

retention (19%), diarrhea (17%), headache (12%), musculoskeletal pain (11%), rash (11%) and pleural effusion (10%).

Unlike ibrutinib that binds to BTK Cys 481, a frequent site of acquired resistance in WM (Xu et al, 2017), dasatinib binds at BTK Thr 474 (Hantschel et al, PNAS 2007). Based on preclinical data, dasatinib also inhibits hematopoietic cell kinase (HCK),. Both HCK and BTK are inhibited at a nanomolar concentration (0.35 nM and 1.4 nM, respectively) (Karaman et al, 2008). HCK is a member of the SRC family of protein tyrosine kinases, and one of the most aberrantly upregulated genes in WM cells (Gutierrez et al, 2007). In myeloma cells, HCK is activated by IL-6 through the IL-6 coreceptor IL-6ST. IL-6 is also a potent growth and survival factor in WM. HCK is an important mediator of WM cells survival, and HCK transcription and activation are enhanced in MYD88 mutated WM cells, also mediated by IL-6 (Yang et al, 2016). HCK expression was significantly higher on primary WM cells when compared to normal non-memory or memory B-cells.

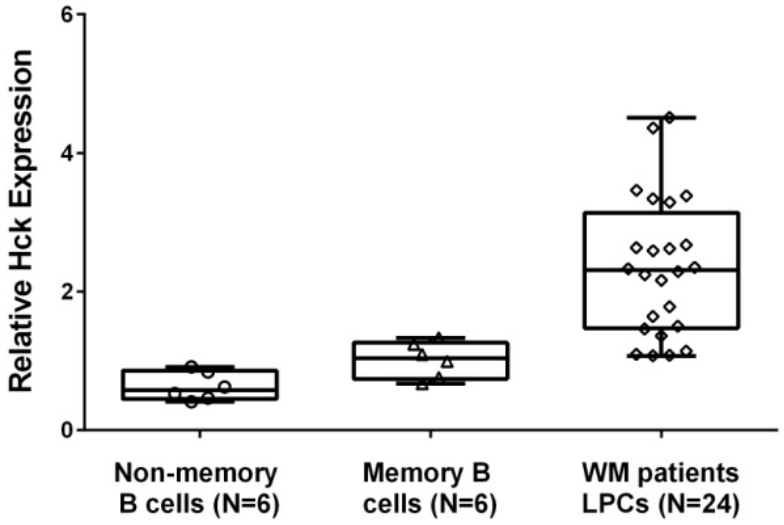


Figure 1. HCK transcription using TaqMan Gene Expression Assay in primary LPCs (CD19+) from MYD88 L265P expressing WM patients, and HD-derived non-memory (CD19+CD27-) and memory (CD19+CD27+) B cells. $P<0.01$ for comparison of WM LPC vs. either HD non-memory or memory B-cells.

Knockdown of HCK reduced the survival of and attenuated BTK, PI3K/AKT and MAPK/ERK signaling in mutated MYD88 WM cells. Specifically, dasatinib induced apoptosis in mutated MYD88 WM and DLBCL cell lines.

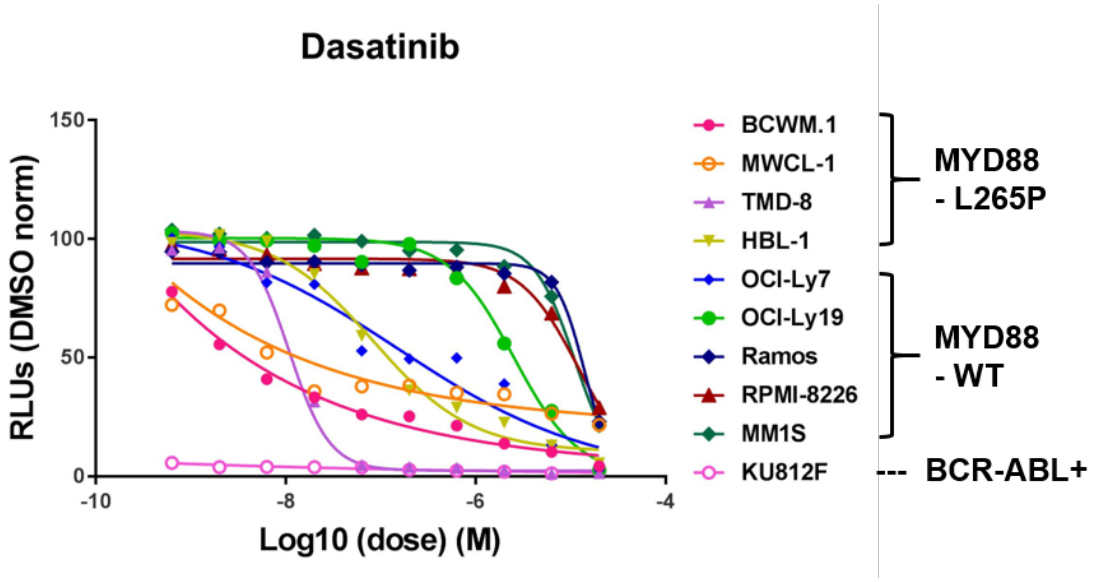


Figure 2. Dose-dependent survival determined by CellTiter-Glo Luminescent Cell Viability Assay for mutated (BCWM.1, MWCL-1, TMD-8, HBL-1, and OCI-LY3) and WT (OCI-LY7, OCI-LY19, Ramos, and RPMI 8226) MYD88 cells following treatment with dasatinib for 72 hours.

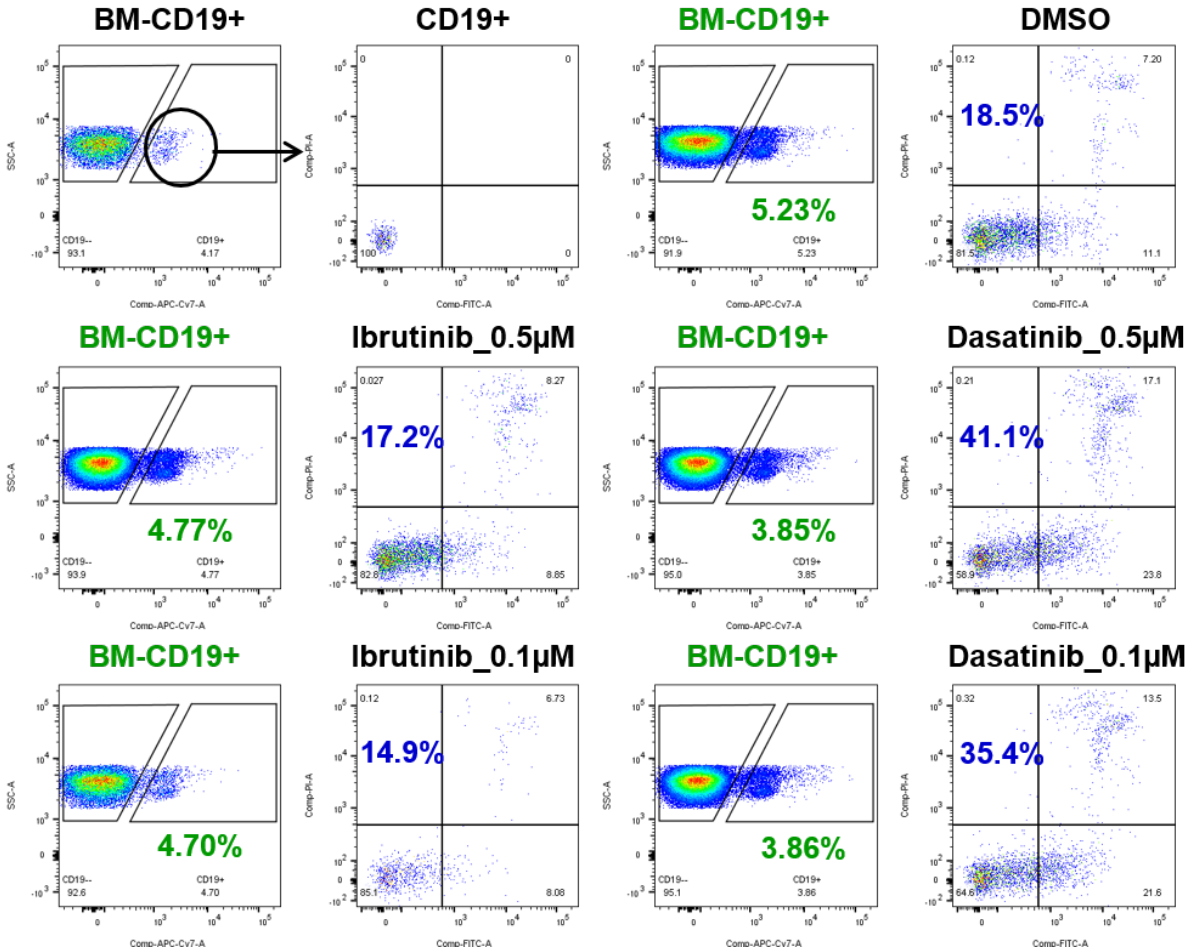


Figure 3. Phosflow analysis showing changes in pHCKTyr411 following treatment of MYD88-mutated primary WM cells with 0.1 mM and 0.5 mM of ibrutinib or dasatinib for 30 minutes.

Of specific interest is the preclinical efficacy of dasatinib in BTK mutated WM cell lines.

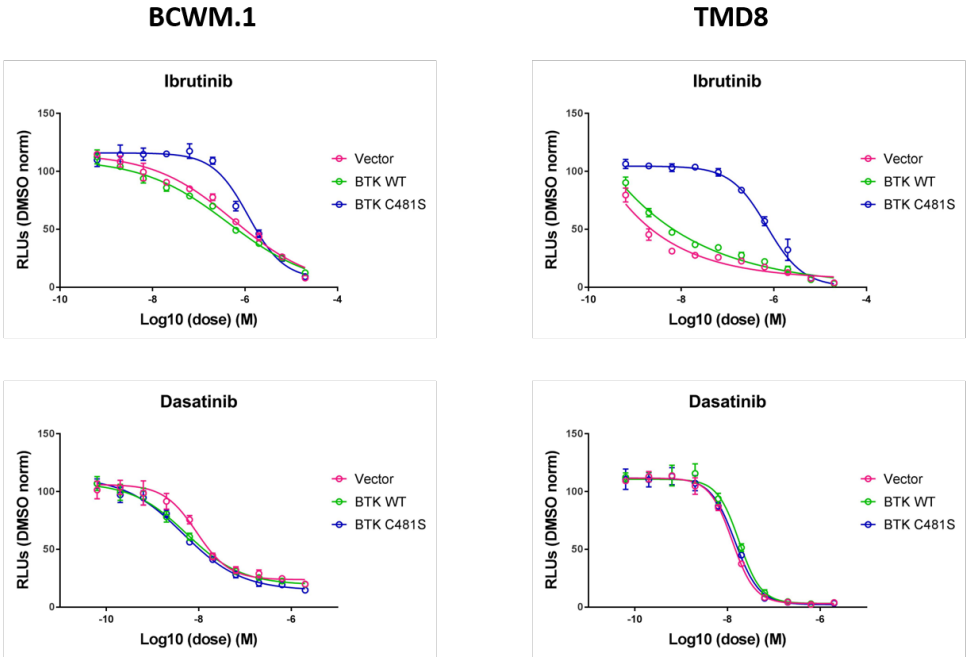


Figure 4. Dose-dependent survival determined by Cell Titer-Glo Luminescent Cell Viability Assay for BTK-mutated and BTK WT cells following treatment with dasatinib for 72 hours.

2.2.1 Nonclinical Studies of Dasatinib

Drug discovery and nonclinical pharmacology studies showed that dasatinib:

- Kills BCR-ABL dependent leukemic cell lines, including those resistant to imatinib due to kinase domain mutations or overexpression of SRC family kinases
- Is effective against all imatinib-resistant kinase domain mutations tested to date, except T315I
- Has average cytotoxic potency 380-fold higher than imatinib in 4 imatinib naive CML cell lines
- Inhibited proliferation of numerous cancer cell lines that express activated SRC or c KIT
- Is active against several human CML xenografts in SCID mice at doses below MTD
- Is active against several susceptible human solid cancer models in nude mice
- Potently inhibits VEGF-stimulated proliferation and migration in HUVECs
- Has potent bone anti-resorptive activity
- Non-covalent inhibitor of BTK at Thr 474, different that BTK Cys 481 that ibrutinib binds
- Blocks SRC family members including HCK, FYN
- Triggers killing of MYD88 mutated ABC DLBCL cells, including ibrutinib resistant BTK Cys481 mutant expressing cells in vitro and in xenograft models independent of BTK itself (Scuoppo et al, 2019).

Dasatinib was 260-, 8-, 60-, and >1000-fold more potent than imatinib versus BCR-ABL, c-KIT, PDGF receptor β, and SRC kinases, respectively.

Dasatinib inhibited cellular SRC autophosphorylation in several solid tumor cell lines that highly express c-SRC. These include P815 for mastocytoma; PC3, PC3/M, MDA PCa 2b, DU145 for prostate cancer; WiDr, LOVO, SW 480, 2C8, GEO for colon cancer; MDA MB 231 for breast cancer; RD1 for rhabdomyosarcoma, and A549 for lung cancer.[1] Assays in SCLC cell lines demonstrated that dasatinib inhibited stem cell factor (SCF)-driven proliferation with a potency range of 110 nM to 220 nM. The concentration range of dasatinib required to inhibit c-KIT phosphorylation was in range with that needed to inhibit cellular proliferation.[1]

Dasatinib exhibited *in vivo* antitumor activity in a broad spectrum of solid tumor types in nude mice. In mice, twice daily (BID) regimens 5-days-on and 2-days-off for 14 to 25 days were well-tolerated with no sign of overt toxicity at doses up to 50 mpk/adm and were equally efficacious as continuous dosing regimens.[1]

Nonclinical Toxicology

The toxicity of dasatinib was evaluated in a spectrum of nonclinical safety studies, including single- and repeat-dose oral toxicity studies in mice, rats, dogs, and monkeys; a battery of in vitro and in vivo genotoxicity studies; a 2-year rat carcinogenicity study; reproductive and development toxicity studies in rats and rabbits; and a range-finding study that evaluated the feasibility of conducting a definitive perinatal and postnatal development study in rats. Based on these nonclinical evaluations, there were no findings that would preclude the administration of dasatinib to humans. However, women of childbearing potential should be advised to avoid becoming pregnant while taking dasatinib.

Clinical Pharmacokinetics

Dasatinib is rapidly absorbed following oral administration in subjects with leukemia. The median time to reach the maximum observed concentration (Cmax) ranged from 0.45 to 3.2 hours postdose (overall median = 1 hour). The observed food effects were not clinically relevant. Dasatinib has an apparent volume of distribution of 2,505 L, suggesting extensive distribution to the extravascular space.

Dasatinib is extensively metabolized in humans by cytochrome P450 3A4. Unchanged dasatinib represented 29% of circulating radioactivity in plasma after a 100-mg dose of [14C]-labeled dasatinib was administered to 8 healthy subjects. Elimination is predominantly in the feces, mostly as metabolites. Following a single oral dose of [14C]-labeled dasatinib, approximately 85% of the dose was recovered in the feces within 10 days, and approximately 4% of the administered radioactivity was recovered in the urine. Unchanged dasatinib accounted for 19% and 0.1% of the administered dose in feces and urine, respectively, with the remainder of the dose being metabolites.

The overall mean half-life of dasatinib was approximately 3 to 5 hours and was not affected by dose administration interval (ie, QD or BID), disease status (ie, CP, AP, or CML), or duration of dosing (ie, PK evaluated on various study days following the initiation of dosing). The dasatinib dose-exposure (AUC) relationship is approximately proportional in the dose range of 15 to 240 mg/day, suggesting linear PK. However, the 90% confidence intervals (CIs) are wide, indicating that the variability in the AUC is high. The geometric mean accumulation index ranged from

1.01 to 1.6 between Days 5/8 and 26/29, and no consistent dose-related trends were observed in the accumulation of dasatinib after repeated administration.

Population PK analyses indicated that dasatinib can be administered without dose adjustment for body weight, age, gender, or race. The clearance of dasatinib did not change with time, and no evidence of autoinhibition or autoinduction was observed. There were no statistically significant or clinically relevant differences in dasatinib PK between subjects with newly diagnosed CP CML and subjects with CP CML who had been previously treated with imatinib.

2.2.2 Clinical Safety

The data presented in Table 2 reflect exposure to dasatinib in 2182 patients with leukemia in clinical studies (starting dosage 100 mg once daily, 140 mg once daily, 50 mg twice daily, or 70 mg twice daily). The median duration of therapy was 11 months (range 0.03–26 months).

The majority of dasatinib-treated patients (1,864 [85%]) experienced at least 1 drug-related adverse reaction at some time. Drug was discontinued for adverse reactions in 14% (296/2182) of subjects. Drug related AEs leading to discontinuation in any 1 category occurred in ≤1% of the subjects with the exception of pleural effusion (85/2182; 4%). In subjects with chronic phase CML, drug-related pleural effusion accounted for discontinuation in 52 of the 1150 subjects. Only 1 subject in the 100 mg QD group had discontinuation due to drug-related pleural effusion compared with 35 subjects in the 70 mg BID group. In subjects with advanced phase CML or Ph+ ALL, drug-related pleural effusion accounted for discontinuation in 33 of the 1032 subjects. Six subjects in the 140 mg QD group had discontinuation due to drug-related pleural effusion compared with 27 subjects in the 70 mg BID group.

Overall, 59% (1287/2182) of subjects across all disease phases reported SAEs (any grade). Drug-related SAEs were reported in 53% (681/2182) of subjects. In subjects with chronic phase CML, notable common drug-related AEs included dyspnea, pleural effusion, congestive heart failure, febrile neutropenia, and thrombocytopenia. In most cases, a lower proportion of subjects in the 100 mg QD group reported drug-related SAEs than subjects in the 70 mg BID or other dose groups. In subjects with advanced phase CML or Ph+ ALL, notable common drug-related AEs included dyspnea, pleural effusion, diarrhea, and hematological toxicities. In most cases, there was little difference in these SAEs between the 140 mg QD and 70 mg BID groups. Rates of severe drug-related pleural effusion were lower in the 140 mg QD group (3%) vs the 70 mg BID (6%).

2.2.3 Clinical Efficacy with Dasatinib

Efficacy data with a minimum of 5 years of follow-up for dasatinib are presented in the SPRYCEL USPI and SmPC as the representative product labels for the adult indications of CP and 2 years for AP and BP CML and Ph+ ALL with resistance to or intolerance of imatinib. Efficacy data with 7 and 5 years of follow-up for Studies CA180034 and CA180035, respectively, are presented in this IB. (Efficacy results for Studies CA180034 and CA180035 are presented by randomized treatment group.)

Efficacy in Subjects with Chronic Phase CML

Data from the Phase 3 Study CA180056 (dasatinib showed statistically significant improvement in cCCyR at 12 months compared to imatinib) led to the approval of dasatinib in the treatment

of naive CP CML in USPI and SmPC. Long-term efficacy after 5 years of follow-up supports the durability of the high response rates of dasatinib demonstrated in the primary. After a minimum of 5 years of follow-up, a similar percentage of treated subjects discontinued study treatment for reasons other than study closure (100/258 [38.8%] in the dasatinib group and 96/258 [37.2%] in the imatinib group).

Efficacy in Subjects with Advanced Phase CML and PH+ ALL Resistant to or Intolerant of Imatinib

StudyCA180034

In Study CA180034 (a randomized 2 × 2 Phase 3 study in subjects with CP CML who were resistant to or intolerant of imatinib), dasatinib demonstrated efficacy with both BID and QD dosing; however, the 100-mg QD dosing schedule showed improved tolerability and a reduced incidence of key side effects such as myelosuppression and pleural effusion. This efficacy result was confirmed at the 7-year follow-up

Based on these preclinical findings, dasatinib as a single agent can prove to be safe and effective in patients with symptomatic WM.

StudyCA180035

In Study CA180035 (a randomized Phase 3 study in subjects with AP CML, BP CML [myeloid or lymphoid], or Ph+ ALL who were resistant to or intolerant of imatinib), dasatinib demonstrated efficacy with both BID and QD dosing; however, the QD dosing schedule was associated with fewer dose reductions and interruptions and had fewer subjects reporting fluid retention-related AEs of all grades (including pleural effusion, pulmonary edema, pericardial effusion, and congestive heart failure [CHF]) as compared with the 70-mg BID dosing schedule. This result was confirmed at the 5-year follow-up.

2.3 Rationale

Dasatinib inhibits BTK, which is the main substrate of ibrutinib. Ibrutinib is already approved by the US FDA and the EMA for its use in patients with symptomatic WM. In a preclinical comparative study, nanomolar concentrations of dasatinib induced higher cell killing levels than ibrutinib in primary WM cells.

The binding of dasatinib to BTK is likely non-covalent and occurs at a different location than C481S, a hot spot associated with ibrutinib resistance in patients with CLL, MCL and WM. Therefore, dasatinib might prove to be effective in patients who would otherwise be resistant to ibrutinib. Preclinical data from our laboratory supports that dasatinib overcomes ibrutinib resistance associated with BTK C481S mutations in WM cell lines. About 50% of participants progressing on ibrutinib have the BTK Cys 481 mutation, and 5-10% have the PLCG2 mutation, which can be subclonal to the BTKCys 481 mutations (27, 28, 29). Other mutation and structural losses have recently been described in WM patients, including 6q and 8p deletions encompassing regulators of BTK, MYD88/NFKB, and apoptosis. Dasatinib is a known inhibitor of SRC family members including HCK, a key driver of growth and survival of mutated MYD88 through multiple growth pathways including BTK, AKT, ERK and SYK (Yang et al, 2016; Munshi et al, 2020). Therefore, dasatinib may block MYD88 tiggered growth through non-covalent binding to

BTK but also by inhibition of SRC family members (Yang et al, 2016; Scuoppo et al, 2019); see Figure 5 below.

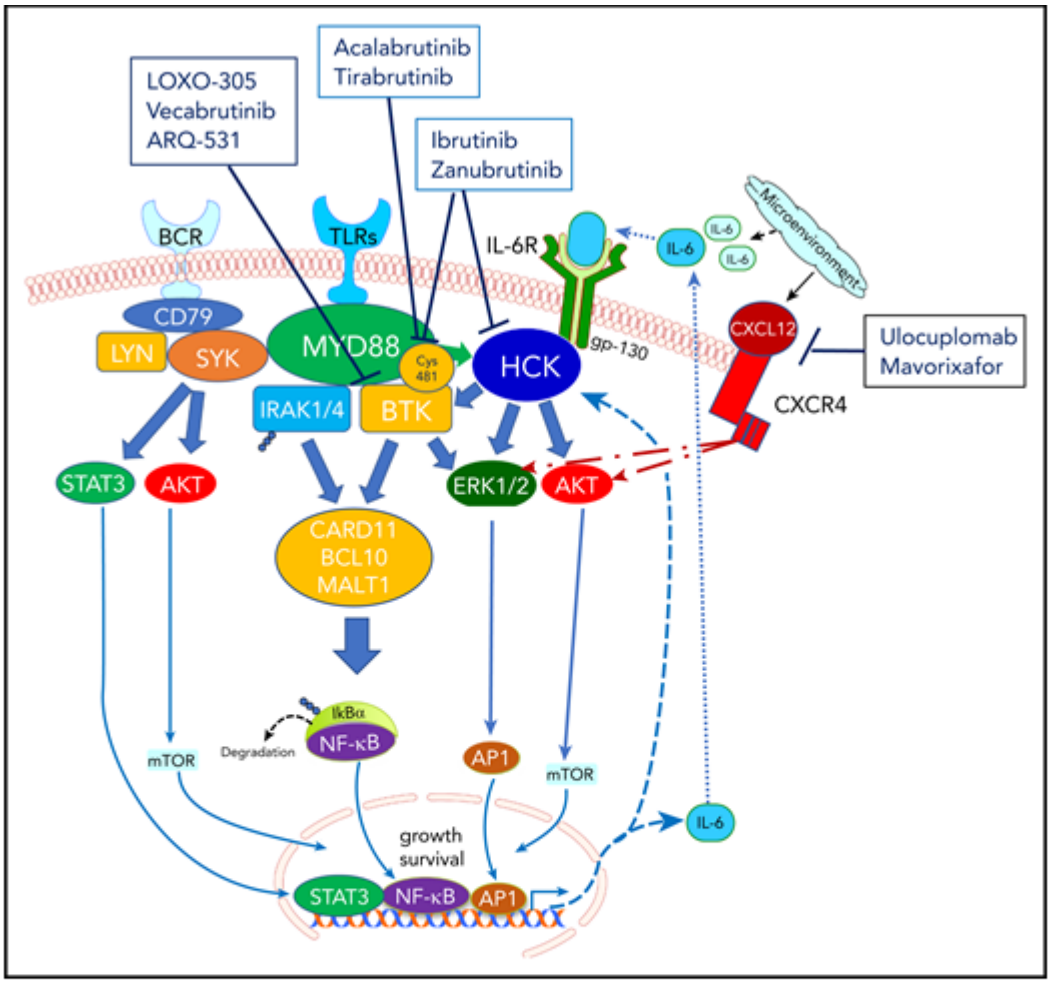


Fig 5. Prosurvival signaling triggered by mutated MYD88 in WM. Dasatinib targets both BTK and HCK. For BTK, dasatinib binds at Thr-474, by non-covalent interactions. Ibrutinib and Zanubrutinib are covalent BTK-inhibitors that bind to Cys 481 on BTK, a frequent site of acquired resistance in WM. Other non-covalent inhibitors including LOXO-305, vecabrutinib and ARQ-531 are in development. Modified from Kapoor and Treon, Blood 2020.

Hypothesis

Single agent dasatinib is associated with a high overall response rate in WM patients who are progressing on ibrutinib.

2.4 Correlative Studies Background

MYD88 L265P is a recently identified somatic mutation present in >90% of WM patients but in <5% of patients with other related processes such as CLL or MZL with plasmacytic differentiation or IgM myeloma (Treon 2012). Many groups have now validated the presence of this somatic mutation in WM patients. MYD88 L265P supports growth and survival of WM cells through both IRAK1 and IRAK4 (Treon 2012) as well as by activation of Bruton tyrosine kinase (BTK) (Yang 2013). Based on these findings, we conducted a clinical trial using the BTK inhibitor ibrutinib in 63 patients with relapsed/refractory WM (Treon 2015; 2020). In this study, ibrutinib was well tolerated and effective. Median hemoglobin improved from 10.5 g/dl to 14.2 g/dl and IgM decreased from 3520 mg/dl to 821 mg/dl. Bone marrow involvement decreased from 70% to20% with a best ORR of 91% and a major response rate of 77%. The major response rate was 97% for patients with wild-type CXCR4 vs. 68% in those with WHIM-like CXCR4 mutations. Decreases in serum IgM as well as improvements in hemoglobin were greater in patients with wild-type CXCR4.

In recent studies, the MYD88 and CXCR4 mutational status are predictive of clinical status, response to therapy and survival outcomes (Treon et al, 2014; 2020). Activating MYD88 as well as nonsense and frameshift WHIM-like CXCR4 somatic mutations are common in Waldenström macroglobulinemia. CXCR4 nonsense mutations are present in aggressive cases including hyperviscosity syndrome, and MYD88 status is a determinant of survival (Treon et al, 2018). The MYD88 L265P mutational analysis by allele-specific PCR and CXCR4 mutational analysis by Sanger sequencing will be performed by the Bing Center for Waldenström Macroglobulinemia in Boston, MA for research purposes. Eligibility for the study includes known MYD88 mutation and will be based on testing at a CLIA certified laboratory. If the participant has had MYD88 mutation testing previously performed by a CLIA accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for eligibility determination.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate. Screening evaluations including consent, physical exam, and laboratory

assessments will be done within 30 days prior to Cycle 1 Day 1. Bone marrow biopsy & aspirate, and CT C/A/P will be done within 90 days prior to Cycle 1 Day 1.

3.1.1 Clinicopathological diagnosis of Waldenstrom's Macroglobulinemia

3.1.2 Known tumor expression of mutated MYD88 performed by a CLIA certified laboratory.

3.1.3 At least one previous therapy, with ibrutinib as the most recent treatment. Participants may remain on ibrutinib therapy during screening. A 1 day washout before starting dasatinib is required.

3.1.4 Documented disease progression on last regimen (ibrutinib) per the Sixth International Workshop on WM (Owen et al, 2013). One or more of the following:

3.1.4.1 25% increase in serum IgM level with at least 500 mg/dL absolute increase from nadir with re-confirmation

3.1.4.2 Progression of clinically significant disease related symptoms

3.1.5 Symptomatic disease meeting criteria for treatment using consensus panel criteria from the Second International Workshop on WM (Kyle et al, 2003). One or more of the following:

3.1.5.1 Constitutional symptoms
3.1.5.2 Progressive or symptomatic lymphadenopathy or splenomegaly
3.1.5.3 Hemoglobin <10 g/dL
3.1.5.4 Platelet count <100 k/uL
3.1.5.5 Symptomatic peripheral neuropathy
3.1.5.6 Systemic amyloidosis
3.1.5.7 Renal insufficiency
3.1.5.8 Symptomatic cryoglobulinemia

3.1.6 Age 18 years or older

3.1.7 Measurable disease, defined as presence of immunoglobulin M (IgM) paraprotein with a minimum serum IgM level of > 2 times the upper limit normal.

3.1.8 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

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

3.1.10 Men must agree to use a latex condom during sexual contact with a female of childbearing potential (FCBP) even if they have had a successful vasectomy.

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

- Absolute neutrophil count ≥500/ uL (Growth factor not permitted)
- Platelets ≥50,000/ uL (Platelet transfusion not permitted)
- Hemoglobin ≥ 7 g/dL (RBC transfusion permitted)
- Total bilirubin ≤ 2 mg/dL
- Potassium ≥ LLN
- Magnesium ≥ LLN
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- Estimated GFR ≥ 30 ml/min

3.1.12 Able to swallow pills.

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

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

3.2 Exclusion Criteria

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

3.2.1 Lactating or pregnant women.

3.2.2 Participants who are receiving any other investigational agents.

3.2.3 Prior therapy with BCR-ABL inhibitors.

3.2.4 Known CNS lymphoma.

3.2.6 Symptomatic hyperviscosity requiring urgent therapy.

3.2.5 Human Immunodeficiency Virus (HIV), active infection with Hepatitis B Virus (HBV), and/or Hepatitis C Virus (HCV).

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, pleural or pericardial effusion, unstable angina pectoris, cardiac arrhythmia, QT Prolongation, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Prolonged QTc interval on pre-entry electrocardiogram (> 450 msec)

3.2.8 History clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes

3.2.9 Known history of alcohol or drug abuse

3.2.10 On any active therapy for other malignancies with the exception of topical therapies for basal cell or squamous cell cancers of the skin.

3.2.11 History of non-compliance to medical regimens.

3.2.12 Treatment with strong CYP3A4/5 inhibitors or inducers

3.2.13 Participants who are taking St. Johns Wort must discontinue at least 5 days before starting dasatinib.

3.2.14 Treatment with H2 Antagonists and proton pump inhibitors

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION

4.1 General Guidelines for DF/HCC Institutions

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

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

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

5. TREATMENT PLAN

5.1 Treatment Regimen

Dasatinib treatment will be administered daily in four-week cycles for up to 24 cycles. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Dasatinib	Premedications: n/a Precautions: Avoid simultaneous administration with antacids. Adminster antacid at least 2 hours prior to or 2 hours after dasatinib	100mg	PO	Daily (QD)	28 days (4 weeks)
Up to 24 cycles					

5.2 Pre-Treatment Criteria

C1D1 results do not need to meet eligibility parameters. Day 1 chemistry and hematology laboratories must be reviewed prior to treatment.

Participants must meet the following criteria on Day 1 of all cycles with clinic visits:

- No grade 3 nausea, vomiting, or diarrhea (if persistent despite optimal antiemetic and/or antidiarrheal therapy)
- No non-hematologic grade 3 toxicities
- Neutrophil count $\geq$ 500/uL (growth factor permitted to retreat)
- Platelet count
    - $\geq$ 25,000 uL in the absence of bleeding (platelet transfusion permitted to retreat)
    - $\geq$ 50,000 uL in the presence of bleeding (platelet transfusion permitted to retreat)

5.3 Agent Administration

Participants will self-administer dasatinib 100 mg orally once daily. The tablets should be taken consistently either in the morning or the evening, swallowed whole. The tablets must not be crushed or cut. Dasatinib can be taken with or without a meal. Participants will be instructed not to take antacids within two hours of a dose of dasatinib. Dasatinib will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken.

If a dose of dasatinib is not taken at the scheduled time, it can be taken as soon as possible within 6 hours, with a return to the normal schedule the following day. The participant should not take extra tablets to make up a missed dose.

If vomiting occurs within 30 minutes of taking dasatinib, that dose may be repeated.

Dose reductions due to toxicity will be permitted on information seen in Section 6.

5.4 Definition of Dose-Limiting Toxicity (DLT)

The following will be considered a DLT if occurring during the 1st Cycle of Therapy:

- ≥ Grade 4 hematologic toxicity (anemia, neutropenia, or thrombocytopenia)
- Any grade 5 hematologic or non-hematologic toxicity
- Any grade 4 non-hematologic toxicity, including vomiting or diarrhea
- Any other ≥ Grade 3 adverse event not due to underlying disease, except for Grade 3 infection, easily reversible asymptomatic laboratory abnormalities, and nausea, vomiting, or diarrhea controlled by medications.
    - Grade 3 vomiting or diarrhea can only be excluded if the participant does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours.
    - Reversible asymptomatic laboratory abnormalities may be excluded only if they are correctable to <grade 3 within 72 hours.

Management and dose modifications associated with the above adverse events attributed to dasatinib are outlined in Section 6.

If two participants experience a DLT or if any participant has a grade 5 treatment-related DLT enrollment will be stopped.

5.5 General Concomitant Medication and Supportive Care Guidelines

Participants will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the participant about any new medications he/she is or has taken after the start of the study drug.

Anti-emetics are permitted if clinically indicated. Standard supportive care medications are permitted. All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to participants.
- No anticancer agents other than the study medication should be given to participants. If such agents are required for a patient, then the patient must first be withdrawn from the study.
- Growth factors (i.e. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) can be administered prophylactically, except to confirm eligibility, and may be prescribed at the discretion of the treating physician for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria.
- Transfusions (red blood cells, platelets) can be administered for treatment-related hematologic events in accordance with ASCO guidelines, and to meet re-treatment criteria. Transfusions of RBCs can be administered to meet eligibility criteria, but platelet transfusions are not permitted to meet eligibility criteria.
- Use of H2 Antagonists and Proton Pump Inhibitors (PPIs) is prohibited. These drugs may decrease dasatinib drug levels. Consider antacids instead.

- Avoid grapefruit and Seville oranges.
- Concurrent administration of dasatinib and strong CYP3A4/5 inhibitors and inducers is prohibited. Examples of Strong inhibitors/inducers of CYP3A4/5 are in Table 5-1.

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

Inhibitors of CYP3A4/5		**Inducers of CYP3A4/5**
Strong inhibitors:		**Strong CYP3A inducers:**
Boceprevir	Nefazodone	Avasimibe
Clarithromycin	Nelfinavir	Carbamazepine
Cobicistat	Ritonavir	Enzalutamine
Conivaptan	Paritaprevir/ritonavir	Mitotane
Danoprevir/ritonavir	combinations	Phenytoin
Elvitegravir/ritonavir	Posaconazle	Rifampin
Idelalisib	Squinavir	St. John's wort
Indinavir	Telaprevir	
Itraconazole	Telithromycin	
Ketoconazole	Tipranavir/ritonavir	
Mibefradil	Voriconazole	
Lopinavir/ritonavir		

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

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for *24 cycles* or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Special mentions:

For participants meeting criteria for disease progression (based on consensus panel criteria for IgM response) but are deemed by the investigator to be clinically benefiting from dasatinib, these individuals will be permitted to continue on protocol therapy at the principal investigator's discretion. Documentation describing the rationale for continuing benefit shall be entered into the medical record. Clinical benefit will be determined by considering clinical data, such as overall participant performance and disposition, complete blood counts, and when necessary, results from

bone marrow biopsies and/or CT scans. In such instances, any new nadir that may result with continued therapy will be used as the study nadir point for this patient. Patients must be on ≥2 consecutive weeks of therapy for determination of a reliable IgM reading for response assessment purposes.

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.7 Duration of Follow Up

Participants will be followed for 2 years after removal from protocol therapy, or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 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 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the event of a non-hematological grade 3 or 4 toxicity such as chest pain, pleural effusion, or pericardial effusion the study drug should be stopped until appropriate diagnostic and therapeutic procedures have been undertaken. Following the resolution of these events to ≤grade 1 dasatinib may be restarted a reduced dose (see Table 6-1 below).

Dose re-escalation is not allowed for dose reduction triggered treatment related toxicities.

Participants with any one of the following must permanently discontinue dasatinib therapy:

- An acute myocardial infarction or any other clinically significant arterial thromboembolic complication
- Patients with confirmed pulmonary artery hypertension
- Any treatment-related Grade 4 non-hematologic toxicity. However, if the patient is deriving clinical benefit from dasatinib, and the toxicity resolves to Grade ≤1, the participant can re-start at a reduced dose after approval by the PI.
- Women who become pregnant or are breast feeding

If a participant requires a dose delay of >28 days, then the participant must be discontinued from the study, unless permitted to resume after discussion with the PI.

Table 6-1 Dasatinib Dose Modification Guidelines

Dose Level	***Dasatinib* Dose**
0	*100 mg PO QD*
-1	*70 mg PO QD*
-2	*50 mg PO QD*

6.1 Dasatinib Dose Adjustments for AEs

Neutropenia	**Management/Next Dose for *Dasatinib***
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	No change in dose. Hold until ≤Grade 2 if infection and/or fever present. Resume at the same dose.
Grade 4	Hold if grade 4 until ≤ Grade 3. Resume at the same dose unless this is a recurring event or takes >7 days to recover at which time the dose should be reduced.
*Administer G-CSF or growth factors for neutropenia as indicated.	

Thrombocytopenia	**Management/Next Dose for *Dasatinib***
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2 if bleeding present. No change in dose in the absence of bleeding. Resume at the same dose.
Grade 4	Hold if grade 4 until ≤ Grade 3. Resume at the same dose unless this is a recurring event or takes >7 days to recover at which time the dose should be reduced.
*Platelet transfusions for thrombocytopenia permitted.	

Non-Hematological Toxicities related to Dasatinib	**Management/Next Dose for *Dasatinib***
≤ Grade 1	• Add supportive care as indicated. Continue dasatinib at the current dose level.
Grade 2	• Add supportive care as indicated. Continue dasatinib at the

Non-Hematological Toxicities related to Dasatinib	**Management/Next Dose for *Dasatinib***
	current dose level.
Grade 3 without optimal prophylaxis or which are easily managed by medical intervention or resolved quickly	• Interrupt dasatinib and add supportive care as indicated • For AEs that are easily managed (e.g., correction of electrolytes) with resolution to baseline or Grade ≤ 1 within 24 hours, dasatinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced • For AEs that require supportive care, the dose should be held while supportive care is initiated and optimized. Then upon resolution of the AE to baseline or Grade ≤ 1, dasatinib may be resumed at either the same dose or with a dose reduction at the discretion of the investigator unless this is a recurring event at which time the dose should be reduced
Grade 3 that occurred despite optimal prophylaxis or is not easily managed by medical intervention	• Interrupt study treatment until recovery to ≤ Grade 1 or baseline, and resume treatment with a dose reduction
Grade 4	• Permanently discontinue study treatment unless determined that the subject is unequivocally deriving clinical benefit. In this case, upon recovery to Grade ≤ 1 or baseline, the subject may be re-treated at a reduced dose that is to be determined by the investigator

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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

7.1.1 Adverse Events List

7.1.1.1 Adverse Event List(s) for Dasatinib

Infections and infestations	
Very common	infection (including bacterial, viral, fungal, non-specified)
Common	pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including uncommon cases with fatal outcomes)
Blood and lymphatic system disorders	
Very Common	myelosuppression (including anemia, neutropenia, thrombocytopenia)
Common	febrile neutropenia
Uncommon	lymphadenopathy, lymphopenia
Rare	aplasia pure red cell

Immune system disorders	
Uncommon	hypersensitivity (including erythema nodosum)
Endocrine Disorders	
Uncommon	hypothyroidism
Rare	hyperthyroidism, thyroiditis
Metabolism and nutrition disorders	
Common	appetite disturbances[a], hyperuricaemia
Uncommon	tumour lysis syndrome, dehydration, hypoalbuminemia, hypercholesterolemia
Rare	diabetes mellitus
Psychiatric disorders	
Common	depression, insomnia
Uncommon	anxiety, confusional state, affect lability, libido decreased
Nervous system disorders	
Very common	headache
Common	neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence
Uncommon	CNS bleeding*[b], syncope, tremor, amnesia, balance disorder
Rare	cerebrovascular accident, transient ischaemic attack, convulsion, optic neuritis, VIIth nerve paralysis, dementia, ataxia
Eye disorders	
Common	visual disorder (including visual disturbance, vision blurred, and visual acuity reduced), dry eye
Uncommon	visual impairment, conjunctivitis, photophobia, lacrimation increased
Ear and labyrinth disorders	
Common	tinnitus
Uncommon	hearing loss, vertigo
Cardiac disorders	
Common	congestive heart failure/cardiac dysfunction*[c], pericardial effusion*, arrhythmia (including tachycardia), palpitations
Uncommon	myocardial infarction (including fatal outcome)*, electrocardiogram QT prolonged*, pericarditis, ventricular arrhythmia (including ventricular tachycardia), angina pectoris, cardiomegaly, electrocardiogram T wave abnormal, troponin increased
Rare	cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis
Not known	atrial fibrillation/atrial flutter
Vascular disorders	
Very common	haemorrhage*[d]
Common	hypertension, flushing
Uncommon	hypotension, thrombophlebitis
Rare	deep vein thrombosis, embolism, livedo reticularis
Respiratory, thoracic and mediastinal disorders	
Very common	pleural effusion*, dyspnoea
Common	pulmonary oedema*, pulmonary hypertension*, lung infiltration, pneumonitis, cough
Uncommon	pulmonary arterial hypertension, bronchospasm, asthma
Rare	pulmonary embolism, acute respiratory distress syndrome
Not known	interstitial lung disease
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain
Common	gastrointestinal bleeding*, colitis (including neutropenic colitis), gastritis, mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, oral soft tissue disorder
Uncommon	pancreatitis (including acute pancreatitis), upper gastrointestinal ulcer, oesophagitis, ascites*, anal fissure, dysphagia, gastroesophageal reflux disease
Rare	protein-losing gastroenteropathy, ileus, anal fistula

Not known	fatal gastrointestinal haemorrhage*
Hepatobiliary disorders	
Uncommon	hepatitis, cholecystitis, cholestasis
Skin and subcutaneous tissue disorders	
Very common	skin rash[e]
Common	alopecia, dermatitis (including eczema), pruritus, acne, dry skin, urticaria, hyperhidrosis
Uncommon	neutrophilic dermatosis, photosensitivity, pigmentation disorder, panniculitis, skin ulcer, bullous conditions, nail disorder, palmar-plantar erythrodysesthesia syndrome, hair disorder
Rare	leukocytoclastic vasculitis, skin fibrosis
Not known	Stevens-Johnson Syndrome[f]
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain
Common	arthralgia, myalgia, muscular weakness, musculoskeletal stiffness, muscle spasm
Uncommon	rhabdomyolysis, osteonecrosis, muscle inflammation, tendonitis, arthritis
Renal and urinary disorders	
Uncommon	renal impairment (including renal failure), urinary frequency, proteinuria
Pregnancy, puerperium and perinatal conditions	
Rare	abortion
Reproductive system and breast disorders	
Uncommon	gynecomastia, menstrual disorder
General disorders and administration site conditions	
Very common	peripheral oedema[g], fatigue, pyrexia, face oedema[h]
Common	asthenia, pain, chest pain, generalised oedema*[i], chills
Uncommon	malaise, other superficial oedema[j]
Rare	gait disturbance
Investigations	
Common	weight decreased, weight increased
Uncommon	blood creatine phosphokinase increased, gamma-glutamyltransferase increased
Injury, poisoning, and procedural complications	
Common	contusion

a. Includes decreased appetite, early satiety, increased appetite.

b. Includes central nervous system haemorrhage, cerebral haematoma, cerebral haemorrhage, extradural haematoma, haemorrhage intracranial, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, and subdural haemorrhage.

c. Includes brain natriuretic peptide increased, ventricular dysfunction, left ventricular dysfunction, right ventricular dysfunction, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased and ventricular failure, left ventricular failure, right ventricular failure, and ventricular hypokinesia.

d. Excludes gastrointestinal bleeding and CNS bleeding; these adverse reactions are reported under the gastrointestinal disorders system organ class and the nervous system disorders system organ class, respectively.

e. Includes drug eruption, erythema, erythema multiforme, erythrosis, exfoliative rash, generalised erythema, genital rash, heat rash, milia, miliaria, pustular psoriaisis, rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin irritation, toxic skin eruption, urticaria vesiculosa, and vasculitic rash.

f. In the post-marketing setting, individual cases of Stevens-Johnson syndrome have been reported. It could not be determined whether these mucocutaneous adverse reactions were directly related to SPRYCEL or to concomitant medications.

g. Gravitational oedema, localised oedema, oedema peripheral.

h. Conjunctival oedema, eye oedema, eye swelling, eyelid oedema, face oedema, lip oedema, macular oedema, oedema mouth, orbital oedema, periorbitalo edema, swelling face.

i. Fluid overload, fluid retention, gastrointestinal oedema, generalised oedema, oedema, oedema due to cardiac disease, perinephric effusion, post procedural oedema, visceral oedema.

j. Genital swelling, incision site oedema, oedema genital, penile oedema, penile swelling, scrotal oedema, skin swelling, testicular swelling, vulvovaginal swelling.

7.1.1.1.1 Warnings and Precautions

Myelosuppression

Treatment with dasatinib is associated with severe (NCI CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia. Their occurrence is more frequent in patients with advanced CML or Ph+ ALL than in chronic phase CML. Complete blood counts should be performed weekly for the first 2 months and then monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding dasatinib temporarily or dose reduction.1 In a Phase 3 dose-optimization study in patients with chronic phase CML, Grade 3 or 4 myelosuppression was reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily.

Bleeding Related Events

Severe CNS hemorrhages, including fatalities, occurred in ≤ 1% of patients receiving dasatinib. Severe gastrointestinal hemorrhage occurred in 4% of patients and generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients. Most bleeding events were associated with severe thrombocytopenia. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution.)

Patients were excluded from participation in dasatinib clinical studies if they took medications that inhibit platelet function or anticoagulants. In some trials, the use of anticoagulants, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) was allowed concurrently with dasatinib if the platelet count was 50,000 to 75,000. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants.1

Fluid Retention

Dasatinib is associated with fluid retention. In all clinical studies, severe fluid retention was reported in 10% of patients, including pleural and pericardial effusion reported in 7% and 1% of patients, respectively. Severe ascites and generalized edema were each reported in < 1% of patients. Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray. Severe pleural effusion may require thoracentesis and oxygen therapy. Fluid retention events were typically managed by supportive care measures that include diuretics or

short courses of steroids. (Incidences in this paragraph reflect drug-related adverse reactions based on investigator's attribution).24

In the Phase 3 dose-optimization study in patients with chronic phase CML, fluid retention events were reported less frequently in patients treated with 100 mg once daily than in patients treated with 70 mg twice daily.

QT Prolongation

A comprehensive evaluation of data from Phase 2 studies (N = 865) examined the possible effect of dasatinib on ECG parameters, particularly the QTc interval. The mean QTc interval changes from baseline using Fridericia's method (QTcF) were 4 to 6 msec; the upper 95% confidence intervals for all mean changes from baseline were < 7 msec. On-study, a total of 5 subjects (< 1%) reported a QTcF > 500 msec; 1 of these 5 subjects reported a QTcF > 500 msec on both Day 1 and Day 8. No events of torsade de pointes were reported.

Nine of the 1150 subjects with chronic phase CML had QTc prolongation reported as an adverse event. Of these 9 subjects, 7 were considered related to drug. None of the 9 subjects who reported QTc prolongation were from the 100 mg QD group compared with 8 subjects from the 70 mg BID group. Ten of the 1032 subjects with advanced disease had QTc prolongation reported as an adverse event. Of these 10 subjects, 7 were considered drug-related. All 10 of the subjects who reported QTc prolongation were from the 70 mg BID group. Overall, of the 2182 subjects treated with dasatinib, 21 (1%) subjects across the studies reported a QTcF > 500 msec.

7.1.1.1.2 Laboratory Abnormalities with Dasatinib

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced CML or Ph+ ALL than in chronic phase CML. Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption and/or reduction; permanent discontinuation of treatment occurred in 1% of patients. Grade 3 or 4 elevations of transaminase or bilirubin and Grade 3 or 4 hypocalcemia and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML and Ph+ ALL. Elevations in transaminase or bilirubin were usually managed with dose reduction or interruption.

Patients developing Grade 3 or 4 hypocalcemia during the course of dasatinib therapy often had recovery with oral calcium supplementation. In the Phase 2 randomized study, the frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was 63%, 56%, and 19%, respectively, in the dasatinib group and 39%, 14%, and 8%, respectively, in the imatinib group. The frequency of Grade 3 or 4 hypocalcemia was 4% in the dasatinib group and 0% in the imatinib group. Laboratory abnormalities reported in the Phase 3 dose-optimization study in patients with chronic phase CML are shown in Table 4.

Table 3: CTC Grades 3/4 Laboratory Abnormalities in Clinical Studies

	Chronic Phase[a] (n=1150)	Accelerated Phase (n=502)	Myeloid Blast Phase (n=280)	Lymphoid Blast Phase and Ph+ ALL (n=250)
	Percent (%) of Patients			
Hematology Parameters				
Neutropenia	47	69	80	78
Thrombocytopenia	41	72	82	78
Anemia	19	55	75	46
Biochemistry Parameters				
Hypophosphatemia	10	12	19	20
Hypocalcemia	2	7	16	11
Elevated SGPT (ALT)	1	3	6	7
Elevated SGOT (AST)	1	1	4	5
Elevated Bilirubin	1	1	4	5
Elevated Creatinine	1	2	3	1

[a] The chronic phase data include patients prescribed any dose of dasatinib.

CTC grades: neutropenia (Grade 3 ≥0.5–1.0 × 109/L, Grade 4 < 0.5 × 109/L); thrombocytopenia (Grade 3 ≥10–50 × 109/L, Grade 4 < 10 × 109/L); anemia (hemoglobin ≥65–80 g/L, Grade 4 < 65 g/L); elevated creatinine (Grade 3 > 3–6 × upper limit of normal range (ULN), Grade 4 > 6 × ULN); elevated bilirubin (Grade 3 > 3–10 × ULN, Grade 4 > 10 x ULN); elevated SGOT or SGPT (Grade 3 > 5-20 x ULN, Grade 4 > 20 x ULN); hypocalcemia (Grade 3 < 7.0-6.0 mg/dL, Grade 4 < 6.0 mg/dL); hypophosphatemia (Grade 3 < 2.0-1.0 mg/dL, Grade 4 < 1.0 mg/dL).

7.1.1.1.3 Drug-Related Serious Adverse Events

Overall, 59% (1287/2182) of subjects across all disease phases reported SAEs (any grade). Drug-related SAEs were reported in 53% (681/2182) of subjects. In subjects with chronic phase CML (N = 1150), notable common drug-related AEs included dyspnea, pleural effusion, congestive heart failure, febrile neutropenia, and thrombocytopenia. In most cases, a lower proportion of subjects in the 100 mg QD group reported drug-related SAEs than subjects in the 70 mg BID or other dose groups. In subjects with advanced phase CML or Ph+ ALL (N = 1032), notable common drug-related AEs included dyspnea, pleural effusion, diarrhea, and hematological toxicities. In most cases, there was little difference in these SAEs between the 140 mg QD and 70 mg BID groups. Rates of severe drug-related pleural effusion were lower in the 140 mg QD group (3%) vs the 70 mg BID (6%).

7.1.1.1.4 Drug-Related Deaths

A total of 577 (26%) deaths at any time after the last dasatinib dose occurred in the cohort of 2182 subjects pooled across disease phases. Disease accounted for 304 of the 577 deaths.

In subjects with chronic phase CML (N = 1150), a total of 86 (7%) subjects died. Of these 86 deaths, deaths due to study drug toxicity occurred in 2 subjects (1 due to pulmonary edema,

CHF, neck pain, pleural effusion and 1 due to necrosis of the colon). Both subjects were in the 70 mg BID group.

In subjects with advanced phase CML or Ph+ ALL, a total of 491 (48%) subjects died. Death due to study drug toxicity occurred in 8 subjects.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Overall PI.

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

7.3.3 DF/HCC Adverse Event Reporting Guidelines

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

7.4 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The

Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to BMS Worldwide Safety

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety.

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs and pregnancies must be reported to BMS within 24 hours of learning of the event regardless of causality. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

a) results in death
b) is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
c) requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
d) results in persistent or significant disability/incapacity
e) is a congenital anomaly/birth defect
f) is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
g) Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.
h) Although pregnancy, overdose and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)

- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

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 the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.6 Reporting to Hospital Risk Management

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

7.7 Routine Adverse Event Reporting

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

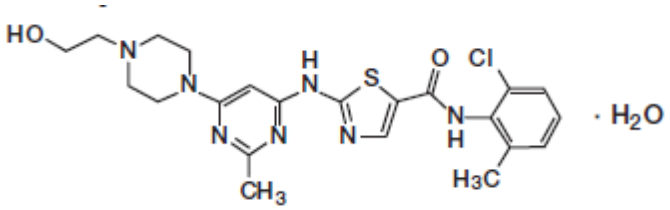
8. PHARMACEUTICAL INFORMATION

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

8.1 *IND Agent #1 Dasatinib*

8.1.1 Description

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C22H26ClN7O2S • H2O, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol. SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

8.1.2 **Form**

Dasatinib is available as 20 mg, 50 mg, 70 mg, 80 mg, 100 mg film-coated tablets.

8.1.3 **Storage and Stability**

Bottles containing dasatinib tablets should be stored at 20° - 25°C. Excursions permitted between 15° and 30°.

8.1.4 **Compatibility**

N/a.

8.1.5 **Handling**

Dasatinib tablets consist of a core tablet (containing the active drug substance), surrounded by a film coating to prevent exposure of pharmacy and clinical personnel to the active drug substance. However, if tablets are inadvertently crushed or broken, pharmacy and clinical personnel should wear disposable chemotherapy gloves. Personnel who are pregnant should avoid exposure to crushed or broken tablets.

8.1.6 **Availability**

Dasatinib is provided by Bristol-Myers Squibb. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

8.1.7 **Preparation**

N/a.

8.1.8 **Administration**

Dasatinib should be self-administered daily by the participant at approximately the same time (morning or evening). Tablets should not be crushed or cut; they should be swallowed whole. Dasatinib may be taken on an empty or full stomach. Participants will be instructed not to take

antacids within two hours of a dose of dasatinib. The dosing time may be adjusted as required. If a participant forgets to take a dose, it may be taken up to 6 hours later. If vomiting occurs within 30 minutes of intake, that dose may be repeated.

8.1.9 **Ordering**

In this protocol, investigational product is Dasatinib, which will be supplied by BMS.

The process for ordering study drug from BMS for the initial shipment and resupply shipments will be managed by the site through completion of a drug shipment request form, which will be provided by BMS.

BMS contact details for drug ordering:
Please email the drug supply form with the subject heading "Dasatinib Supply Request" to the following:

Email: **SRCSupply@bms.com**
Fax (to Wallingford, Connecticut USA): 866-227-7229
203-677-6489

8.1.10 **Accountability**

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

8.1.11 **Destruction and Return**

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Laboratory Correlative Studies

9.1.1 Assessment of MYD88 L265P and CXCR4 WHIM genotyping.

An allele-specific polymerase-chain-reaction (PCR) assay will be used to detect $MYD88^{L265P}$, $CXCR4^{WHIM}$ mutation status will be determined by means of Sanger sequencing, and allele-specific PCR will be used to detect $CXCR4^{S338X}$ C→G and C→A mutations in CD19-selected bone marrow cells (Xu et al, 2013; Hunter et al,2014; Treon et al, 2014). Bone marrow aspirate

(approximately 30 cc in 2 heparinized syringes & 1 purple top) will be collected at the screening bone marrow biopsy.

At baseline, the samples will be genotyped for MYD88 and CXCR4 mutations by the Bing Center for WM laboratory. Whole exome sequencing of BM samples will be performed as before to characterize variants including BTK Cys481 mutations associated with ibrutinib resistance (Jimenez et al, 2020). The samples will be used until depletion.

Bing Center address:
450 Brookline Avenue Mayer 5
Boston, MA 02215

10. STUDY CALENDAR

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Screening* ≤ 30days from study entry	**Treatment Phase**[7] **48- four week cycles (4 years)**		**Off Treatment Assessment**	**Follow-Up Phase**
		Cycles 1*, 2 (4 weeks ± 3 days)	Cycles 3, 6, 9, etc. until 24 four week cycles completed (12 weeks± 2 weeks)	Within 4 weeks of completion of entire treatment plan or removal from study ± 2 weeks	Post Treatment; Every 12 weeks ± 2 weeks for 2 years
Physical exams[1], vital signs, weight	X	X	X	X	X
Medical History	X				
ECOG performance status (see Appendix A)	X				

CT of the chest & abdomen / pelvis[2]	X		X[2]		X (if applicable)
Bone marrow biopsy and aspiration[3]	X		X[3]		X (if applicable)
Quantitative serum IgM, IgG, IgA, free light chain assays	X	X	X	X	X
ECG	X				
Serum immuno-electropheresis	X	X	X	X	X
Complete Blood Count plus differential[1,4]	X	X	X	X	X
Coagulation profile: PT, PTT, PT-INR[5]	X				
Chemistry/ Comprehensive Metabolic Panel including: Electrolytes, Renal (BUN, Creatinine, eGFR) and Hepatic function testing [ALT (SGPT), AST (SGOT), Alk phos, total Bilirubin, albumin, and total protein], Magnesium, Phosphorus, Uric acid	X	X	X	X	X
LDH	X				
Pregnancy Test[6]	X				
Beta-2 microglobulin test	X				
Review patient diary		X	X		
HBsAG, HBsAb, HBcAB, HCV, HIV Ab	X				
Adverse event monitoring (see section 6)		X	X	X	

* Labs, Physical exam, vital signs, and weight do not need to be repeated if Cycle 1, Day 1 is within 28 days of Screening. Cycle 1, Day 1 labs, if drawn, do not need to re-confirm eligibility prior to administering first dose.

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

[2]**If CT scans of the chest, abdomen and pelvis have been collected and done within 90 days of Cycle 1 Day 1 they will not be required at the screening visit.** Scans will be **repeated at cycle 6, 12, and EOT, for participants with extramedullary disease at baseline defined as adenopathy >1.5 cm in any axis, and splenomegaly >15 cm in the craniocaudal axis.** Scans will also be repeated to confirm a complete response if the participant has no detectable monoclonal protein and had extramedullary disease at baseline, and at the discretion of the investigator.

[3]Bone marrow biopsy and aspirations are **required at baseline within 90 days of Cycle 1 Day 1, and at cycle 6, 12, and EOT, or at time of progression** Bone marrow biopsy and aspiration may also be done at the investigator's discretion, and at any time to confirm a complete response if the participant has no detectable monoclonal protein. MYD88 and CXCR4 mutation status will

be assessed at baseline only. 10 mL of aspirate will be sent to the Treon Laboratory for whole exome sequencing for variants associated with ibrutinib resistance at baseline.

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

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

[6]For women of child-bearing potential only, a serum pregnancy test will be required at screening.

[7]Please refer to Section 6 for Dose Modifications.

11. MEASUREMENT OF EFFECT

11.1.1 Definitions

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

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

11.1.2 Response Criteria

Complete Response (CR): A complete response (CR) is defined as having resolution of WM

related symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. A complete response requires reconfirmation demonstrating normal serum IgM levels, and absence of IgM paraprotein by immunofixation by a measurement repeated at least 2 weeks later.

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

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

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

Progressive Disease (PD): Progressive disease (PD) is defined as occurring when a greater than 25% increase in serum IgM level occurs with an absolute increase of at least 500 mg/dL from the lowest attained response value, or progression of clinically significant disease related symptom(s). Reconfirmation of the initial IgM increase is required when IgM is the sole criterion for progressive disease confirmation. Death from any cause or initiation of a new anti-neoplastic therapy will also be considered a progression event. An increase of 1 cm in any axis for adenopathy, or 2 cm in the craniocaudal axis of the spleen will be considered evidence of progression of extramedullary disease. Development of Bing Neel syndrome, or other extramedullary disease manifestations, as well as disease transformation will be considered as progressive events.

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

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

11.1.2.1 Time-to-event definition

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of objective disease progression (including initiation of new therapy or death).

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

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

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

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

13. STATISTICAL CONSIDERATIONS

Patients' clinical and pathological characteristics and response to therapy will be presented using descriptive statistics. Median PFS, TTNT and OS times as well as 2-year and 4-year PFS, TTNT and OS rates will be estimated using the Kaplan-Meier method for incomplete observations. Predictive factors for response will be evaluated using logistic and linear regression, when appropriate. Prognostic factors for survival will be evaluated by fitting Cox proportional hazard regression models. Updates on response and survival will be evaluated and presented yearly.

13.1 Study Design/Endpoints

This is a pilot study, aimed to assess the safety and possible efficacy of dasatinib as a salvage therapy after progression on ibrutinib for participants with Waldenstrom Macroglobulinemia. WM patients who progress on ibrutinib have a median of overall survival of 21 months, and new therapeutic strategies are needed to address this. Given the small sample size of this trial, this study is not powered on disease outcomes, but we will collect and descriptively analyze many study elements.

The maximum accrual for this study will be 6 participants. If two participants experience DLTs or any participants have a grade 5 treatment-related DLT then enrollment will be stopped early and the study will be permanently closed.

The following will be considered a DLT if occurring during the 1st Cycle of Therapy:

- $\geq$ Grade 4 hematologic toxicity (anemia, neutropenia, or thrombocytopenia)
- Any grade 5 hematologic or non-hematologic toxicity

- Any grade 4 non-hematologic toxicity, including vomiting or diarrhea
- Any other ≥ Grade 3 adverse event not due to underlying disease, except for Grade 3 infection, easily reversible asymptomatic laboratory abnormalities, and nausea, vomiting, or diarrhea controlled by medications.
    - Grade 3 vomiting or diarrhea can only be excluded if the participant does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours.
    - Reversible asymptomatic laboratory abnormalities may be excluded only if they are correctable to <grade 3 within 72 hours.

Primary Objectives

- To evaluate the toxicity profile of dasatinib in WM patients who progressed on ibrutinib with BTK or PLCG2 mutations.

13.2 Secondary Objectives

- To evaluate the ORR of dasatinib in WM patients who are progressed .
- To evaluate the rate of CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD) and progressive disease (PD) to dasatinib in WM patients who progressed on ibrutinib.
- To evaluate progression-free survival, time to next therapy (TTNT), and overall survival to dasatinib in WM patients who progressed on ibrutinib.
- To evaluate the impact of MYD88 and CXCR4 mutations on response to dasatinib in WM patients who progressed on ibrutinib.

13.3 Sample Size, Accrual Rate and Study Duration

The present pilot study will accrue 6 patients. The total study duration will be approximately 3.5 years, which include 18 months of accrual, 2 years of treatment and 2 years of follow-up.

13.4 Stratification Factors

No stratification factors will be applied for the study.

13.5 Interim Monitoring Plan

The study will be monitored by the DFCI Data Safety Monitoring Committee (DSMC). The DSMC will meet at least two times a year and more often if needed (e.g., for safety review). For each meeting, the study will be reviewed for safety and progress toward completion. Copies of the toxicity reports prepared by the DSMC meetings will be distributed to the Principal Investigator. The Principal Investigator will then distribute to sub-investigators. Any DSMC recommendations for changes to the study will be distributed to the Principal Investigator and then circulated to sub- investigators by the Principal Investigator. No interim analysis of the outcome data is planned.

13.6 Analysis of Primary Endpoints

Primary analyses will be performed in FAS population and will include calculating the proportion of patients having a major response (PR or better). Confidence intervals (95%) around these point estimates will be presented.

13.7 Analysis of Secondary Endpoints

The Per-Protocol Analysis Set (PPS) is defined as all participants from the FAS set who complete the study and are deemed to be protocol-compliant. To be protocol-compiant, a participant must not have any major protocol deviations during the study period. Protocol deviations will be identified prior to database lock and will be listed in the clniical study report. The PPS will be used for secondary assessment of efficacy endpoints.

Secondary analyses will be performed in both the FAS and PPS populations. The time to response, both major (PR or better) and minor response will be estimated using Kaplan Meier methodology with median time plus 25th and 75th percentile time to response along with 95% confidence intervals being provided, as appropriate. Time to progression (TTP) will also be estimated using Kaplan Meier methodology. Best overall response and Very Good Partial Response (>90% reduction in disease burden)/ CR (complete response) will be estimated in both the FAS and PPS populations involving calculating the proportion of patients having an overall response (MR or better). Confidence intervals (95%) around these point estimates will be presented.

13.8 Reporting and Exclusions

13.8.1 Evaluation of Toxicity

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

13.8.2 Evaluation of the Primary Efficacy Endpoint

All participants who have received at least one cycle of therapy are eligible for response assessment. Inevaluable patients for response will be replaced. All conclusions will be based on evaluable participants.

14. PUBLICATION PLAN

Interim study results may be presented at a major scientific meeting (American Society of Hematology, the International Workshop on WM or the International Conference on Malignant Lymphoma).

A full report that will include primary and secondary endpoints will be published in a peer-reviewed journal that meets the requirements of the International Committee of Medical Journal Editors within 24 months of reaching the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable	40	Disabled, requires special care and

	of only limited self-care, confined to bed or chair more than 50% of waking hours.		assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.