A study of brentuximab vedotin (SGN-35) in CD30-positive systemic mastocytosis with or without an associated hematological clonal non-mast cell lineage disease (AHNMD)

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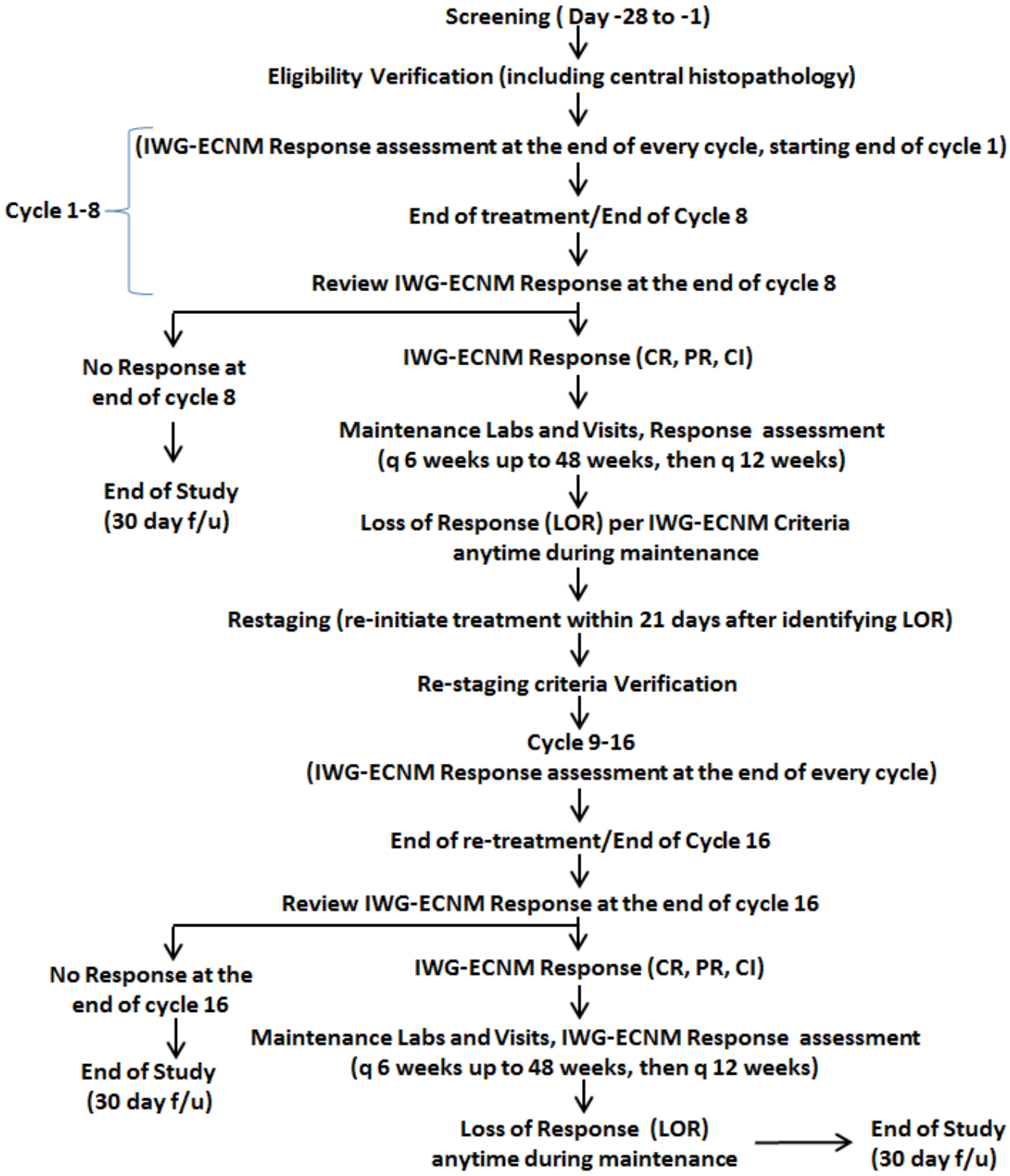
List of abbreviations

2-CdA	2-chlorodeoxyadenosine (cladribine)
ADME	Absorption, distribution, metabolism, and excretion
AE	adverse event
AHNMD	associated hematological clonal non-mast cell lineage disease
ALT	alanine aminotransferase/ glutamic pyruvic transaminase/GPT
AML	Acute Myeloid Leukemia
ANC	Absolute neutrophil count
ASM	Aggressive Systemic Mastocytosis
AST	aspartate aminotransferase/ glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Chemical classification system
b.i.d.	*bis in diem*/ twice a day
BM	bone marrow
CF	Clinical Finding (C-Finding)
CEL	Chronic Eosinophilic Leukemia
CLL	Chronic Lymphocytic Leukemia
CM	Cutaneous mastocytosis
CML	Chronic Myeloid/ Myelogenous Leukemia
CMML	Chronic Myelomonocytic Leukemia
CR	Complete Remission
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DAR	Dosage Administration Record
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DoR	Duration of Response
DXA	Dual x-ray energy assessment
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FSH	Follicular stimulating hormone
GGT	Gamma-Glutamyl-Transferase
GPR	Good Partial Response
HES	Hypereosinophilic Syndrome
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
IC	Inhibitory concentration

ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IIT	Investigator-initiated trial
IN	Investigator notification
INF-α	Interferon-α
INR	International normalized ratio
i.v.	intravenous(ly)
IR	Incomplete Remission
IRB	Institutional Review Board
ISM	Indolent Systemic Mastocytosis
IUD	Intrauterine device
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
MCL	Mast Cell Leukemia
MCS	Extracutaneous mastocytoma
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MinR	Minor Response
MPD	Myeloproliferative disorder
MR	Major Response
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NR	No response
NYHA	New York Heart Association
o.d.	omnia die / once a day
ORR	Overall Response Rate
OS	Overall Survival
PCR	Pure Clinical Response
PD	Progressive Disease
PEP	Primary Efficacy Population
PFS	Progression-free survival
PK	Pharmacokinetics
p.o.	*per os* / by mouth/ orally
PP	Per Protocol
PR	Partial Response
PRO	Patient-reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
QL	Quality of Life
RBC	Red blood cells

REB	Research Ethics Board
SAE	Serious Adverse Event
SCF	Stem Cell Factor
SD	Stable Disease
SOP	Standard Operating Procedure
SM	Systemic Mastocytosis
SOC	System Organ Class
SSC	Study Steering Committee
SSM	Smouldering Systemic Mastocytosis
TD	Transfusion-dependent
t.i.d.	*ter in die* / three times a day
TKI	Tyrosine kinase inhibitor
TSH	Thyroid-stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
US	Ultrasound
VEGF	Vascular endothelial growth factor
WBC	White blood cells

FLOW CHART


Screening (Day -28 to -1)
Eligibility Verification (including central histopathology)
Cycle 1-8
(IWG-ECNM Response assessment at the end of every cycle, starting end of cycle 1)
End of treatment/End of Cycle 8
Review IWG-ECNM Response at the end of cycle 8
No Response at end of cycle 8
End of Study (30 day f/u)
IWG-ECNM Response (CR, PR, CI)
Maintenance Labs and Visits, Response assessment (q 6 weeks up to 48 weeks, then q 12 weeks)
Loss of Response (LOR) per IWG-ECNM Criteria anytime during maintenance
Restaging (re-initiate treatment within 21 days after identifying LOR)
Re-staging criteria Verification
Cycle 9-16
(IWG-ECNM Response assessment at the end of every cycle)
End of re-treatment/End of Cycle 16
Review IWG-ECNM Response at the end of cycle 16
No Response at the end of cycle 16
End of Study (30 day f/u)
IWG-ECNM Response (CR, PR, CI)
Maintenance Labs and Visits, IWG-ECNM Response assessment (q 6 weeks up to 48 weeks, then q 12 weeks)
Loss of Response (LOR) anytime during maintenance
End of Study (30 day f/u)

1 Introduction

1.1 Advanced Systemic Mastocytosis

Mastocytosis is a heterogeneous disease characterized by abnormal growth and accumulation of mast cells in one or more organ systems. The current World Health Organization classification system for mast cell disease defines two major subgroups – cutaneous mastocytosis (CM) and systemic mastocytosis (SM) which are further divided into different disease variants (Vardiman *et al.* 2002, Valent *et al.* 2005, Valent *et al.* 2007).

SM is a condition, defined by multifocal histological lesions in the bone marrow and other extracutaneous organs, together with cytological and biochemical signs of systemic disease (Valent *et al.* 2005). SM can show either an indolent or an aggressive clinical course. Depending on the stage of the disease, infiltration of organs may occur with or without impairment of organ function and patients can shift from one category of mast cell disease into another. In all categories, mediator-related symptoms may occur and may represent a serious clinical problem. Infiltration of organs by mast cells may cause cytopenias, osteolysis, pathologic fractures, hepatosplenomegaly, lymphadenopathy, and malabsorption (Vardiman *et al.* 2002, Valent *et al.* 2005, Valent *et al.* 2007).

ASM and MCL are very rare, comprising only a small proportion of all SM cases. ASM is characterized by a pathologic infiltration of diverse organs by neoplastic mast cells, with resulting organ damage (bone marrow, liver, spleen, gastrointestinal tract, skeletal system). Respective clinical/laboratory findings are called 'Clinical Findings' (C-Findings). In this context, mast cell infiltration with associated organomegaly only (B-Finding(s), as seen in SSM) but no sign of organ damage should not be regarded as C-Finding(s). In contrast to the indolent forms of SM in which the patients can stay for many years or even decades with good prognosis, patients with the aggressive form of SM or MCL have a poor prognosis and are candidates for cytoreductive or targeted therapy to limit organ infiltration and further organ damage (Valent *et al.* 2005, Valent *et al.* 2007, Valent *et al.* 2007, Horny *et al.* 2007).

In approximately 30% of SM patients, an AHNMD (myeloid malignancy) is diagnosed. The subvariant categories of AHNMD include SM-AML (acute myeloid leukemia), SM-MDS (myelodysplastic syndrome), SM-MDS/MPN (MDS/myeloproliferative neoplasm, eg, chronic myelomonocytic leukemia), and SM-HES or SM-CEL (hypereosinophilic syndrome or chronic eosinophilic leukemia). Generally, separate treatment plans for the SM and the AHNMD should be established for these patients. However, the SM and AHNMD may share a common pathophysiologic link, and particular treatments may be useful for both the SM and myeloid malignancy. Although the intent of SM-directed therapy is to target neoplastic mast cells, it may not always be possible to identify whether organ damage is due to the SM or AHNMD component or both. Patients with CEL-associated with the FIPL1-PDGFRα fusion gene may exhibit increased mast cells in the bone marrow but are not classified by the WHO as having systemic mastocytosis. It is recommended that such patients be treated with imatinib (Valent *et al.* 2007) and would not be considered eligible for this protocol.

The most important growth factor for mast cells seems to be stem cell factor (SCF) also termed mast cell growth factor or KIT ligand. SCF induces the development of mast cells from their uncommitted CD34+ progenitors. The effects of SCF on mast cells and mast cell

progenitors are mediated through KIT, a tyrosine kinase receptor (for SCF) encoded by the KIT proto-oncogene. SCF and SCF-dependent activation of KIT are essential to the development and differentiation of mast cells. "Gain-of-function mutations" in the kinase domain of *KIT* are associated with enhanced growth of mast cells and their progenitors. Such mutations (eg, D816V) are frequently detected in patients with SM (Valent *et al.* 2005).

Specific gene defects are well recognized as the oncogenic factors in SM. The *KIT* D816V mutation expressed in neoplastic mast cells is by far the most common and is found in all variants of SM. Highly sensitive methods have detected that >90% of patients with SM carry the D816V *KIT* mutation. Several other *KIT* gene defects have been identified in patients with mast cell disease, but each are likely to be present in less than 5% of diagnosed patients (Sotlar *et al.* 2003, Garcia-Montero *et al.* 2006, Valent *et al.* 2005).

Treatments for SM can be divided into two broad categories (1) those intended to control mast cell mediator-related symptoms (eg, antihistamines, epinephrine, or corticosteroids) and (2) those intended to limit the MC burden (eg, cytoreductive or targeted therapies). Due to the heterogeneous nature of the disease an individualized approach to the treatment strategy is indicated. To date, there is no approved standard therapy to treat SM available and there are only limited options for the treatment of ASM and MCL with the exception of imatinib being approved in the US in *KIT* D816V negative patients or those in whom *KIT* mutation status is unknown.

Interferon-α (IFN-α) combined with or without corticosteroids, or cladribine can elicit response rates in approximately 40% of patients, but almost all are partial in nature and short-lived and limited tolerability led to early discontinuation of treatment in some cases (Kluin-Nelemans HC *et al.* 1992, Worobec et al, 1996, Butterfield JH, et al 1998, Tefferi A, *et al.* 2001, Kluin-Nelemans, *et al.* 2003, Casassus P, *et al.* 2002, Hauswirth *et al.* 2004, Akin and Metcalfe, 2004, Valent *et al.* 2007). In ongoing clinical trials, the *KIT* inhibitor midostaurin can inhibit the imatinib-resistant D816V *KIT* mutation *in vitro*, and has shown preliminary encouraging efficacy in patients with ASM/MCL with a 38% major response rate per Valent Criteria (Gotlib et al, 2010).

1.2 SGN-35 (brentuximab vedotin)

Brentuximab vedotin (SGN-35) is a CD30-directed antibody-drug conjugate (ADC) consisting of three components: 1) the antibody cAC10, specific for human CD30, 2) the highly potent antimicrotubule agent monomethyl auristatin E (MMAE), and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. The biological activity of brentuximab vedotin results from a multi-step process. Binding of the ADC to CD30 on the cell surface initiates internalization of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, a single defined active species, MMAE, is released via proteolytic cleavage. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest, and results in apoptotic death of the CD30-expressing tumor cell.

Two phase 2 studies evaluating the efficacy and safety of brentuximab vedotin as a single agent were performed in patients with relapsed or refractory Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (ALCL). In the pivotal phase 2 study of relapsed or

refractory HL, 75% of patients had an objective response (complete or partial remission) with median duration of approximately 7 months. One-third of patients achieved a complete response (CR). In the phase 2 study of relapsed or refractory systemic ALCL, the objective response rate (ORR) was 86%. Due to few events of progression or death, the median duration of objective response was not estimable; however, the lower limit of the 95% confidence interval (CI) was 36 weeks. Over 50% of patients achieved a CR. Nearly all patients (>90%) in both studies experienced a reduction in tumor volume. Treatment-emergent adverse events (AEs) occurring in ≥20% of HL and systemic ALCL patients in the phase 2 studies were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily Grade 1 or 2, with the exception of neutropenia, for which Grade 3 and Grade 4 events were reported for 13% and 7% of patients, respectively. Similar patterns and incidences of AEs were generally observed for HL and ALCL patients.

Following the recommended intravenous (IV) dose of 1.8 mg/kg every 3 weeks, maximum concentrations were typically observed at the end of infusion. A multi-exponential decline in brentuximab vedotin antibody-drug conjugate (ADC) serum concentrations was observed with a terminal half-life of approximately 4 to 6 days. Exposures were approximately dose proportional. After multiple-dose administration of brentuximab vedotin, steady-state was achieved by 21 days, consistent with the terminal half-life estimate. Minimal to no accumulation was observed with multiple doses at the q3wk (every 3 weeks) schedule.

The primary treatment-related effects of repeat-dose brentuximab vedotin administration to rats and monkeys, bone marrow hypocellularity and lymphoid depletion, and the associated decreases in peripheral blood cells are consistent with pharmacologic disruption of microtubules caused by MMAE. Repeat-dose administration of MMAE caused qualitatively similar effects while no adverse effects were associated with the repeat-dose administration of cAC10. The no-observed-adverse-effect level (NOAEL) for repeat-dose administration of brentuximab vedotin was 0.5 and 1 mg/kg in rat and monkey, respectively. The highest non-severely toxic dose (HNSTD) for repeat-dose administration of brentuximab vedotin was 5 and 3 mg/kg in rat and monkey, respectively. In up to one-month repeat-dose toxicity studies of brentuximab vedotin in rats at doses up to 15 mg/kg, the following target organs were identified: bone marrow (hypocellularity), thymus (lymphoid depletion), spleen (lymphoid depletion), liver (focal coagulative necrosis), intestine (single cell necrosis), testis (seminiferous tubular degeneration), and lung (alveolar histiocytosis) in rat only. Following a 4-week recovery period, all target organ toxicity was reversible except for testicular toxicity. Testicular toxicity in rat was partially resolved following a 16-week off-treatment recovery phase (Seattle Genetics, 2010).

1.3 The CD30 Antigen in Mastocytosis

CD30, a member of the TNF-receptor (TNF-R) superfamily, is a transmembrane glycoprotein receptor and is normally found on the surface of activated T cells but has also been detected

on a variety of cell types of hematopoietic origin. The CD30 antigen has a very low expression on normal cells but is found on the Hodgkin Reed-Sternberg (RS) cells of HL and on ALCL and other T cell lymphoproliferative disorders. While the function of CD30 has not been clearly defined, CD30 has been implicated both in cell death and proliferation(Wahl 2002). The utility of CD30 as a diagnostic marker for malignancies, including HL and ALCL, its limited normal tissue expression profile, and its apoptosis-inducing characteristics have led to the investigation of this antigen as a target for immunotherapy.

Investigators Drs. Karl Sotlar, Hans-Peter Horny, and Peter Valent and colleagues recently identified expression of CD30 in neoplastic mast cells in the majority of patients with advanced SM (11/13, 85%), whereas in most patients with indolent SM, few of the neoplastic mast cells expressed CD30 (Sotlar *et al.* 2011, Valent *et al.* 2011). The mast cell leukemia cell line HMC-1, derived from a patient with aggressive SM also expressed CD30. CD30 was not expressed in bone marrow biopsy samples from patients with reactive mast cell hyperplasia or other myeloid neoplasms. CD30 expression has been observed in some myeloid neoplasms (AML).

1.4 Study Rationale

Advanced forms of systemic mastocytosis (eg, aggressive systemic mastocytosis [ASM] and mast cell leukemia [MCL] with or without an AHNMD) represent a large unmet need. In order to address the challenge of these mast cell disorders, SGN-35 will be assessed in SM patients who express the CD30 antigen on their neoplastic mast cells.

2 Study Objectives

2.1 Primary Objective

To evaluate the response rate to SGN-35 in patients with CD30+ advanced SM (ASM or MCL with or without an AHNMD).

2.2 Secondary Objectives

1. To evaluate the tolerability and safety profile of SGN-35 in patients with SM
2. To evaluate expression of CD30 on neoplastic mast cells before and during therapy with SGN-35
3. To evaluate changes in mastocytosis related symptom scores and QOL using a modified Myeloproliferative Neoplasm Symptom Assessment Form (MPNSAF) (Scherber et al, 2011)
4. To evaluate the duration of response (DoR) and time to response (TTR)
5. To evaluate progression-free survival (PFS) and overall survival

2.3 Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the overall response rate per consensus international response criteria (rate of complete + partial remissions + clinical improvement) (see Appendix G). Response rate per Valent response criteria may be evaluated as part of an exploratory analysis.

2.3.2 Secondary Efficacy Endpoints

- Immunohistochemical expression of CD30 on neoplastic mast cells in core biopsy samples or by flow before SGN-35 treatment and after 4 and 8 cycles of therapy
- Total symptom score and QOL score using a modified Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)
- Duration of response (DoR) is defined as the time from first onset of confirmed response to the date of first documented and confirmed progression or death due to ASM/MCL. Time to response (TTR) is defined as the time from start of treatment until the date of onset of a confirmed response
- Progression-free survival (PFS) is defined as the time from start of treatment to the date of the first documented and confirmed progression or death or institution of new therapy

2.3.3 Secondary Safety Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events
- Laboratory abnormalities

3. Investigational Plan

3.1 Overall study design

This is a phase II study designed to evaluate whether there is a signal of efficacy of SGN-35 in patients with CD30+ advanced SM. Advanced SM is defined as ASM or MCL with or without an AHNMD.

3.2 Discussion of design

Patients will receive open label SGN-35 at a starting dose of 1.8 mg/kg administered as a single IV infusion as on Day 1 of each 21-day cycle as an outpatient. Patients will be treated for eight 21-day cycles. The best response per international response criteria will be recorded by the end of cycle 8. Because responses must last at least 12 weeks, any clinical improvement (CI), partial response (PR), or CR response that commences by the of end of cycle 8, and either persists or evolves into a higher quality response for at least 12 weeks will be counted as a response. Patients who demonstrate a response and subsequently meet criteria for loss of response (LOR) will be permitted to undergo re-staging and re-treatment with up to an additional 8 cycles of SGN-35.

3.3 Study population

3.3.1 Patient population

Patients must have screening evaluations performed within 28 days prior to the first dose of study drug and must meet all inclusion and exclusion criteria. If some histopathologic studies for mast cell disease were performed within 3 months prior to signing the consent, such material can be used in place of or to complement histopathologic studies for screening after discussion between Drs. Gotlib, Verstovsek, and George to ensure sufficient quality and quantity of sample for central histopathologic review and testing. However, any histopathologic studies that were not performed should be undertaken during the screening. The Principal Investigator or his/her designee prior to enrollment must review results of all evaluations, ensuring that all inclusion and exclusion criteria have been satisfied, including central histopathology. In addition, the patient must be thoroughly informed about the study, including the visit schedule and required evaluations. The written informed consent must be obtained prior to enrollment.

3.3.2 Inclusion and exclusion criteria

Inclusion criteria

- Aged ≥ 18 years of age
- Patient must give written informed consent
- ECOG performance status of 0-3 (Appendix A)
- Life expectancy > 12 weeks
- Meeting the following laboratory values:
    - AST and ALT ≤ 2.5 x Upper Limit of Normal (ULN) (Exception: ≤ 5 x ULN, if elevation is considered related to ASM/MCL)
    - Serum direct bilirubin ≤ 1.5 x ULN; if considered related to ASM/MCL ≤ 3 x ULN
    - Serum creatinine ≤ 2.0 mg/dL
    - Creatinine clearance (CrCl) ≥ 30 mL/min

- A diagnosis of SM per 2008 WHO Criteria (see Appendix B)
- Neoplastic mast cells must express CD30 by immunohistochemistry or flow cytometry (histopathologic determination made centrally by Dr. Tracy George)
- Patients with ASM and MCL (diagnostic criteria in Appendix C) with or without an AHNMD are required to have at least one of the eligible organ damage findings as defined by the international consensus response criteria
- Both females of childbearing potential and males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 30 days following the last dose of study drug.
- Females of childbearing potential must have a negative serum or urine B-hCG pregnancy test result within 7 days prior to the first dose of SGN-35. Females of non-childbearing

potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.

Exclusion criteria

- Patients unwilling or unable to comply with the protocol.
- Any other concurrent severe known disease (except carcinoma in-situ) concurrent severe and/or uncontrolled medical condition (eg, uncontrolled diabetes, or active uncontrolled infection) which could compromise participation in the study.
- History of another primary malignancy that has not been in remission for at least 3 years. (The following are exempt from the 3-year limit: non-melanoma skin cancer, fully excised melanoma in situ [Stage 0], curatively treated localized prostate cancer, and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on PAP smear.)
- Patients with cardiovascular disease including congestive heart failure Grade 3 or 4 according to the NYHA classification, left ventricular ejection fraction of < 50%, myocardial infarction within previous 6 months and poorly controlled hypertension.
- Women who are pregnant or lactating.
- Patients with ≥ Grade 2 neuropathy
- Patients with a known hypersensitivity to any excipient contained in the drug formulation.
- Confirmed prior diagnosis of HIV infection or active viral hepatitis.
- Patients presenting with an AHNMD requiring immediate cytoreductive therapy or targeted drugs (eg, AML).
- Patients who have received any investigational agent, chemotherapy, interferon-α, or 2-chlorodeoxyadenosine (2-CdA, cladribine) within 30 days prior to Day 1.
- Patients who have received hematopoietic growth factor support within 14 days of Day 1 of SGN-35
- Use of prednisone (or equivalent corticosteroid dose) for SM up to 10 mg/day or its equivalent is allowed, but it cannot have been started during screening. Patients who are on prednisone up to 10 mg/day for medical problems unrelated to SM are also permitted on study.
- Patients with the FIP1L1-PDGFRα fusion even with resistance to imatinib (such patients are no longer defined as systemic mastocytosis by the WHO).
- Patients who have received any treatment with SGN-35 prior to study entry.
- Patients who have had any surgical procedure, excluding central venous catheter placement or other minor procedures (eg, skin biopsy) within 14 days of Day 1.
- Prior treatment with bleomycin

4 TREATMENT

4.1 Treatment Administered (SGN-35)

Investigational drug will be supplied in an open-label manner. Details of study treatment preparation, administration, and storage are described in the Pharmacy Manual.

4.2 Investigational Study Drug SGN-35

4.2.1 Description

Brentuximab vedotin is an ADC composed of a CD30-targeted chimeric monoclonal antibody (cAC10) that is covalently linked, via an enzyme-cleavable linker, to the anti-tubulin agent MMAE. cAC10 has a typical structure of the human IgG1 subclass. Brentuximab vedotin is produced by the chemical conjugation of MMAE to cAC10. Each antibody molecule has, on average, two of its interchain disulfides reduced and the resulting cysteine residues alkylated with SGD-1006 Intermediate (enzyme-cleavable inker + MMAE), leading to a molar ratio of 4 drug molecules per antibody.

Brentuximab vedotin is a heterogeneous mixture of a range of drug-load variants and isoforms. The overall average drug-to-antibody mole ratio (MR_D) is approximately 4. The calculated molecular mass for the nominal form of brentuximab vedotin is approximately 153 kDa.

Pharmaceutical Properties

4.2.1.1. Pharmaceutical properties. Brentuximab vedotin is a sterile, preservative-free, white to off-white lyophilized cake or powder, supplied in single-use vials. Brentuximab vedotin drug product is reconstituted with water for injection (WFI), United States Pharmacopeia (USP). The reconstituted brentuximab vedotin drug product is a clear to slightly opalescent, colorless solution with no visible particulate matter. The reconstituted solution is subsequently diluted in sterile 0.9% Sodium Chloride for Injection, USP, 5% Dextrose Injection USP, or Lactated Ringer's Injection USP, for IV administration.

Brentuximab vedotin is the USAN and the INN assigned to SGN-35. Drug product vials may be labeled as SGN-35 or as brentuximab vedotin; the 2 names can be used interchangeably.

4.2.1.2. Formulation. Each vial contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The drug product vial is reconstituted with the appropriate amount of Sterile Water for Injection. The pH of reconstituted product is approximately 6.6.

4.2.2 Dose and Administration

Study treatment must not be administered as an IV push or bolus. Study treatment will be administered by outpatient IV infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. In the absence of infusion toxicities, the infusion rate for all patients should be calculated in order to achieve a 30-minute infusion period. Study treatment will be administered through a dedicated IV line and cannot be mixed with other medications.

The dose of study treatment is 1.8 mg/kg. Chemical and physical stability of the reconstituted brentuximab vedotin drug product has been demonstrated for 24 hours. Opened and reconstituted vials should be used immediately. If not used immediately, the in-use storage should not be longer than 24 hours. In case infusion is interrupted, the interruption cannot be more than 24 hrs from the time of reconstitution of the drug.

Patients with treatment-associated Grade 2 peripheral neuropathy will follow dose modification as specified in **Table 1** in **Section 4.2.5**. **Dosing is based on patient weight on Cycle 1 Day 1** according to the institutional standard; however, doses will be adjusted for patients who experience a ≥ 10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams (Seattle Genetics, 2010).

Patients will be observed on day 1 for close monitoring of potential side effects of drug therapy and/or disease-related symptoms due to mast cell mediator release (eg, hypotension, anaphylactic shock) for at least 60 minutes after completion of the infusion. Intensive care equipment (eg, crash cart) and/or facilities must be readily available for these trial patients.

4.2.3 Required Pre-medication and Post-medication

Routine premedication should not be administered prior to the first dose of study treatment. However, patients who experience a Grade 1 or 2 infusion-related reaction may receive subsequent study treatment with premedication as described in **Section 4.2.4** below.

4.2.4 Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of study treatment. The infusion is to be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed for at least 60 minutes following the first infusion of study treatment. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institutional standards. This includes adjusting the infusion time if necessary. Medications for infusion-related reactions should be readily available.

Patients who experience a Grade 1 or 2 infusion-related reaction may receive premedication for the current or future potential infusion reactions consisting of acetaminophen(650 mg orally) and diphenhydramine (25 to 50 mg orally or 10 to 25 mg IV) or according to institutional standards, administered 30 to 60 minutes prior to each 30-minute infusion.

4.2.5 Dose Modifications

Intra-patient dose reduction to 1.2 mg/kg will be allowed depending on the type and severity of toxicity. **Table 1** describes the recommended dose modifications for study treatment-associated toxicity (toxicity with suspected relationship to SGN-35).

Peripheral Neuropathy: Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.2 mg/kg. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 peripheral neuropathy, SGN-35 should be discontinued.

Neutropenia: Neutropenia should be managed by dose delays and reductions. The dose of SGN-35 should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of SGN-35 to 1.2 mg/kg may be considered.

Acute Pancreatitis: Acute pancreatitis has been identified as an important potential risk associated with brentuximab vedotin dosing. Dosing should be held until a diagnosis of acute pancreatitis has been excluded if clinically suspected.

The start of the next cycle may be delayed for up to 30 days if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle (**Table 1**). Delays of greater than 30 days are prohibited without approval of the Principal Investigator of the entire study, Dr. Jason Gotlib.

Doses reduced for treatment-related toxicity should not be re-escalated.

If 4 out of the 11 patients experience emergent drug-related Grade 3 or 4 non-hematologic toxicity, the study will be placed on hold for safety review, and if restarted upon study amendment, the starting dose of therapy for subsequent patients would be no more than 1.2 mg/kg.

Table 1. Dose Reduction Algorithms for Non-Hematologic and Hematologic Toxicity With Suspected Relationship to SGN-35

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-Hematologic	Continue at same dose level.	Continue at same dose level, except in the event of Grade 2 neuropathy. For Grade 2 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce the dose to 1.2 mg/kg and resume treatment. If Grade 2 neuropathy recurs at a dose of 1.2 mg/kg, the patient should be discontinued from study.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then resume treatment at the same dose level. [a] If the toxicity has not returned to ≤ Grade 1 after holding the dose for 30 days, then the patient should be discontinued from the study. If the same Grade 3 toxicity recurs, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce to the 1.2 mg/kg/level. [a] For patients with recurrence of the same Grade 3 toxicity, the patient should be discontinued from the study. For Grade 3 neuropathy, withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce the dose to 1.2 mg/kg and resume treatment. If Grade 3 neuropathy recurs at a dose of 1.2 mg/kg, the patient should be discontinued from study.	Withhold dose until toxicity is ≤ Grade 1 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment. [a] If the toxicity has not returned to ≤ Grade 1 after holding the dose for 30 days, then the patient should be discontinued from the study For patients with recurrence of the same Grade 4 toxicity at a dose of 1.2 mg/kg, the patient should be discontinued from the study For Grade 4 neuropathy, SGN-35 should be discontinued.
Hematologic	Continue at same dose level.	Continue at same dose level.	• The dose of SGN-35 should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia. In patients with recurrent Grade 4 neutropenia despite the use of growth factors, discontinuation or dose reduction of SGN-35 to 1.2 mg/kg may be considered. • Dose interruption for anemia will not be undertaken. If patients have Grade 2 to 3 of these events at baseline only Grade 4 cytopenias suspected to be related to study drug will be considered as hematologic toxicity. [b] Obtain weekly labs until lab returns to baseline or Grade 2. • G-CSF for treatment of neutropenic fever may be used, but not for treatment of neutropenia alone, nor for infection prophylaxis in the setting of neutropenia.	

[a] Patients who develop emergent Grade 3 or 4 electrolyte laboratory abnormalities will have the dose of SGN-35 reduced to 1.2 mg/kg in subsequent cycles. If the same Grade 3 or 4 electrolyte abnormalities re-occur, SGN-35 will be discontinued.

[b] Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

4.3 Treatment Discontinuation

Any patient discontinuing study medication prematurely must have the reason categorized on the CRF as one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. unsatisfactory therapeutic effect
5. subject's condition no longer requires study treatment
6. protocol violation
7. subject withdrew consent
8. lost to follow-up
9. administrative problems
10. death

Patients who discontinue the study due to a study drug-related adverse event must be followed weekly for four weeks, or until resolution or stabilization of the event, whichever occurs first.

Patients discontinuing prematurely are to be followed every 6 months for survival until study closure or death of the patient.

4.4 Concomitant therapy

In general, the use of any concomitant medication/therapies deemed necessary for patient supportive care and safety are permitted provided they are documented in the patient records. A list of medications which may be used to treat mediator-related symptoms are listed in **Appendix D**. All medications taken within 30 days of the first dose of study drug and all concomitant medications/therapies must be recorded on the Concomitant/Non-Drug Therapy CRF.

Women will avoid breast-feeding, and all women of childbearing potential will be required to use barrier contraception for the duration of the study and for 3 months post study.

Other anti-cancer agents including chemotherapy, radiation therapy, or biologic response modifiers are not permitted during the study. No other investigational drug is allowed during the study. Hematopoietic growth factors are not permitted during study (except G-CSF for neutropenic fever). Prophylaxis may be used for the prevention of nausea and vomiting and is at the discretion of the investigator.

Other anti-cancer agents including chemotherapy, radiation therapy, or biologic response modifiers are not permitted during the study. The exception is the use of hydroxyurea to control a proliferative leukocyte count related to a concurrent myeloid neoplasm (eg, CMML, or other MDS/MPN, or MPN associated with advanced SM). No other investigational drug is allowed during the study. Hematopoietic growth factors are not permitted during the study

(except G-CSF for neutropenic fever). The exception is the use of erythropoiesis stimulating agents (with or without IV iron) in patients who are Jehovah's witnesses and for religious reasons are not permitted to undergo treatment with blood products. Prophylaxis may be used for the prevention of nausea and vomiting and is at the discretion of the investigator.

During treatment with SGN-35, glucocorticoids can be used in the event of appropriate need, as outlined in **Appendix D**, "Mediator Drugs to Ameliorate Symptoms Related to Systemic Mastocytosis."

4.4.1 Cytochrome P450 Metabolism and Drug- Interactions

Because SGN-35 is primarily metabolized by CYP3A enzymes, any drug known to inhibit or induce CYP3A4 will likely interact with SGN-35. The extent is normally more profound with CYP3A4 inhibitors than with inducers. Where possible, investigators should refrain from choosing to administer CYP3A4/5 inducers to patients on study prior to initiation, and during treatment with SGN-35. In particular, investigators should NOT give the combination of two such agents in patients receiving SGN-35, such as antifungal azoles plus erythromycin or azithromycin. In addition, prior to initiation of SGN-35, and during treatment, concomitant use of the following CYP3A4 *substrates* is discouraged: alprazolam, astemazole, atorvastastin, cervistatin, chlorpheniramine, diazepam, indinavir, lovastatin, midazolam, nelfinavir, progesterone, ritonavir, saquinavir, tacrolimus, terfenadine, triazolam, and the CYP3A4 inducers modafinil, rifabutin, and rifampin. A list of inhibitors and inducers is provided in **Appendix E**.

4.5 Treatment compliance

Records of study drug used, doses, and intervals between visits will be kept during the study. Where appropriate, patients will receive treatment with study drug as outpatients. Patients will be asked to record any symptoms experienced as well as other medications taken. Dosing information for SGN-35 must be documented. Any change of dose, missed doses or dose interruptions must be recorded.

4.6 Visit schedule and assessments

4.6.1 Visit and assessment schedule (see next page)

Evaluations

Pretreatment (Screening)

- Complete medical history including transfusion history in prior 12 weeks
- Prior and current medication list
- Physical exam with spleen measurement
- ECOG performance status
- Vital signs (temperature, heart rate, breathing rate, blood pressure, height, weight)
- 12 lead ECG

- Magnetic resonance imaging (MRI) or computed tomography (CT) scan of the abdomen/pelvis with and without contrast including 3D spleen and liver volumes
- Bone marrow aspirate and biopsy with cytogenetics, flow cytometry, *KIT* mutation status
- Chest x-ray (2 views PA and lateral)
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase, PT, PTT **(Please refer to section 4.8.1 for detailed lab evaluations)**
- Pregnancy test (women of child bearing potential)

Day 1 of Cycles 1 to 8 (+/- 3 days):

- Evaluate for adverse events
- Interval medical history including transfusion history
- Physical exam, including measurement of your spleen, weight, and vital signs
- Current medications
- ECOG performance status
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests (with phosphorus on Cycle 1 Day 1 only), serum tryptase, PT, PTT **(Please refer to section 4.8.1 for detailed lab evaluations)**
- Pregnancy test (women of child bearing potential)
- Drug infusion
- Response assessment per IWG-MRT-ECNM criteria (starts Cycle 2 Day 1)

For Cycle 5 Day 1 (End of cycle 4) also need to complete the following:

- MRI or a CT scan of the abdomen/pelvis with and without contrast including 3D spleen and liver volumes
- Chest X-ray-2 views PA and lateral (only if disease-related finding(s) were found at baseline)
- Bone marrow aspirate and biopsy with cytogenetics, flow cytometry, *KIT* mutation status

Phosphorus will be additionally done on Cycle 1 Day 1; Cycle 1 Day 3; and Cycle 1 Day 8 only, for complete evaluation of tumor lysis.

Day 3 of Cycle 1

- Serum chemistries/liver function tests and phosphorus
- Evaluate for adverse events

Days 8 and 15 of Cycle 1 (+/- 3 days)

- Evaluate for adverse events
- Hematology
- Serum chemistries/liver function tests and phosphorus

Day 10 of Cycles 2-8 (+/- 3 days)

- Hematology
- Evaluate for adverse events

End-of-Treatment (End of Cycle 8) Visit

- Evaluate for adverse events
- Interval medical history including transfusion history
- Current medications
- Physical exam, including measurement of spleen, weight, and vital signs
- ECOG performance Status
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase, PT, PTT **(Please refer to section 4.8.1 for detailed lab evaluations)**
- Pregnancy test (women of child bearing potential)
- MRI or CT of abdomen/pelvis with and without contrast including 3D spleen and liver volumes
- Chest x-ray 2 views - PA and lateral (only if disease related finding(s) were found at baseline)
- Bone marrow aspirate and biopsy with cytogenetics, flow cytometry, *KIT* mutation status
- Response assessment per IWG-MRT-ECNM criteriaDrug Accountability

End of Study (EOS) Visit - if no response to the study drug after 8 cycles of treatment, one follow-up visit about 30 days after the end-of-treatment visit

- Evaluate for adverse events

- Interval medical history including transfusion history
- Current medications
- Physical exam, including measurement of spleen, weight, and vital signs
- ECOG performance status
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase **(Please refer to Section 4.8.1 for detailed lab evaluations)**
- Pregnancy Test (women of child bearing potential)
- Response assessment per IWG-MRT-ECNM criteria

Follow-up visits - if patient did exhibit a response to the study drug after 8 cycles of treatment according to protocol response criteria, follow-up visits and labs every 6 weeks until 48 weeks from beginning of treatment will occur, then every 12 weeks.

- Evaluate for adverse events
- Interval medical history including transfusion history
- Current medications
- Physical exam, including measurement of spleen, weight, and vital signs
- ECOG performance status
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase **(Please refer to Section 4.8.1 for detailed lab evaluations)**
- Bone Marrow aspirate and biopsy, cytogenetics, flow cytometry, *KIT* mutation status (at week 48, then every 24 weeks)
- MRI or CT of abdomen/pelvis with and without contrast including 3D spleen and liver volumes (at week 48, then every 24 weeks)
- Drug accountability
- Response assessment per IWG-MRT-ECNM criteria

Re-Staging if Loss of Response (LOR) (Day -21 to Day -1)

- Interval medical history including transfusion history
- Current medication list
- Physical exam with spleen measurement
- ECOG performance Status
- Vital signs (temperature, heart rate, breathing rate, blood pressure, weight)

- Magnetic resonance imaging (MRI) or computed tomography (CT) scan of the abdomen/pelvis with and without contrast including 3D spleen and liver volumes
- Bone marrow aspirate and biopsy with cytogenetics, flow cytometry, *KIT* mutation statusChest x-ray (2 views – PA and lateral)
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase, **(Please refer to section 4.8.1 for detailed lab evaluations)**
- Pregnancy test (women of child bearing potential)
- Evaluate for adverse events

Re-Treatment Cycles 9 – 16 for patients who exhibit loss of response

- Repeat schedule of original cycles 1, and 2-8 except coags

End-of-Re-treatment (End of Cycle 16) Visit

- Evaluate for adverse events
- Interval medical history including transfusion history
- Current medications
- Physical exam, including measurement of spleen, weight, and vital signs
- ECOG performance Status
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase, PT, PTT **(Please refer to section 4.8.1 for detailed lab evaluations)**
- Pregnancy test (women of child bearing potential)
- MRI or CT of abdomen/pelvis with and without contrast including 3D spleen and liver volumes
- Chest x-ray (2 views-PA and lateral) (only if disease related finding(s) were found at re-staging)
- Bone marrow aspirate and biopsy with cytogenetics, flow cytometry, *KIT* mutation status
- Response assessment per IWG-MRT-ECNM criteria
- Drug Accountability

End of Study (EOS) Visit - if no response to the study drug after 16 cycles of treatment, one follow-up visit about 30 days after the end-of-treatment visit should be undertaken. This is identical to the EOS visit for non-responders at the end of C8

Follow-up visits - if patient did exhibit a response to the study drug after 16 cycles of treatment according to protocol response criteria, follow-up visits and labs every 6 weeks until 48 weeks from beginning of re-treatment. Then every 12 weeks.

- Evaluate for adverse events

- Interval medical history including transfusion history
- Current medications
- Physical exam, including measurement of spleen, weight, and vital signs
- ECOG performance Status
- MPN-SAF modified for mast cell symptoms
- Hematology, chemistries/liver function tests, serum tryptase **(Please refer to section 4.8.1 for detailed lab evaluations)**
- Bone Marrow aspirate and biopsy, cytogenetics, flow cytometry, *KIT* mutation status (at week 48 from day 1 of re-treatment, then every 24 weeks)
- MRI or CT of abdomen/pelvis with and without contrast including 3D spleen and liver volumes (at week 48 from re-treatment, then every 24 weeks)
- Response assessment per IWG-MRT-ECNM criteria

There will not be any additional treatments after completion of the drug infusion at start of cycle 16. Patient will come for follow up visits per the schedule above as long as they show response. At the time of loss of response, patient will have an end of study visit (with the same assessments as at the end of study (EOS) visit for patients with no response at end of cycle 8 or 16) and will be taken off the study.

Long-term survival:

All patients will be followed every 6 months for survival until study closure or death of the patient.

Table 2. Visit and Assessment Schedule

		Assessments within +/- 3 days											
	Screen	**Cycle 1**				**Cycle 2-8**		**End of Treatment (EOT) (@ completion of 8 cycles of therapy)**	**Day +30 after EOT for non-responders (g)**	**Maintenance labs and visits after 8 cycles for ongoing responders (h)**	**Re-Staging for pts who exhibit loss of response (LOR)**	**Re-Treatment Cycles 9-16 [a] for pts who exhibit loss of response (LOR)**	**Long Term Survival** (j)
Evaluation	Day -28 to Day -1	Day 1 **(b)**	Day 3 (can be local)	Day 8 (can be local)	Day 15 (can be local)	Day 1	Day 10 (can be local)	(EOT)	(EOS)	Labs and visits q 6 weeks up to week 48; then q 12 weeks	Day -21 to Day -1	Repeat schedule of original cycles 1, 2-8 and EOT (except PT, PTT)	
Informed consent/eligibility criteria	X												
Complete medical history	X												
Interval medical history		X				X		X	X	X	X		
Prior and concomitant medications	X	X				X		X	X	X	X		
Transfusion history in prior 12 weeks	X	X				X		X	X	X	X		
Vital signs, physical exam, body weight, height[(i)]	X[(i)]	X				X		X	X	X	X		
ECOG performance status	X	X				X		X	X	X	X		
MPN-SAF, QOL questionnaires	X	X				X		X	X	X	X		
12-lead ECG	X												
Hematology [(c)]	X	X		X	X	X	X	X	X	X	X		
Serum chemistries/liver function tests [(c)]	X	X	X	X	X	X		X	X	X	X		
Serum tryptase level	X	X				X		X	X	X	X		
PT and PTT	X	X				X		X					
Pregnancy test	X	X				X		X	X		X		
Chest x-ray (2 views-PA and Lateral)[(d)]	X					X[(d)]		X[(d)]			X		
BM aspiration, cytogenetics, flow cytometry, core biopsy, and *KIT* mutation analysis[(e)]	X					X [(e)]		X[(e)]		X [(e)]	X		
MRI (or CT) abdomen/pelvis with and without contrast including 3-D spleen and liver volumes [(f)]	X					X[(f)]		X [(f)]		X[(f)]	X		
Measurement of spleen by palpation	X	X				X		X	X	X	X		
Drug accountability assessment		X				X		X		X			

Administer study drug during visit		X				X							
Record Adverse Events		X	X	X	X	X	X	X	X	X	X		
Response assessment per IWG-MRT-ECNM Criteria						X		X	X	X			

[a] For patients demonstrating loss of response (LOR) after completion of 8 cycles of therapy, re-treatment for up to an additional 8 cycles (eg, cycles 9-16) may be undertaken. Before re-treatment, **patients should undergo all re-staging studies as shown in the initial screening period, except that a 12-lead EKG and coagulation studies (PT and PTT) are not required. The re-staging period should be completed within 21 days (+/- 3 days) between identifying a loss of response (LOR) and re-initiating treatment. Cycles 9-16 study drug administration and labs/procedures will be conducted on a schedule identical to cycles 1 and 2-8 with an end of treatment (EOT) visit at the completion of cycle 16 of therapy except PT and PTT which will NOT be performed with cycles 9-16, end of treatment (EOT) visit at the completion of cycle 16, or the end of study (EOS) visit.**

[b] Day 1 labs do not need to be repeated if obtained during screening within 72 hours of day 1. Patient infusion on cycle 1, day 1 as well as additional cycles will occur in an outpatient infusion center.

[c] Refer to section 4.8.1 for the labs that should be obtained for hematology and chemistries/liver function tests.

[d] If disease-related findings are found on chest x-ray (2 views PA and lateral) (eg, pleural effusion), then an x-ray will be performed at the end of cycles 4 and 8 or EOT, whichever comes first, and at the time of progressive disease or loss of response (LOR). Chest X-ray (2 views-PA and lateral) will also be performed at the time of re-staging. If disease-related findings are found on chest x-ray (eg, pleural effusion) at the time of re-staging, then an x-ray will be performed at the end of cycles 12 and 16 or EOT, whichever comes first, and at the time of progressive disease or loss of response (LOR). Interval chest x-rays can be performed at the discretion of the investigator.

[e] Besides screening, marrows will be performed at the end of cycles 4 and 8 or EOT, whichever comes first, and at the time of progressive disease or loss of response (LOR). A repeat bone marrow aspirate and biopsy should be performed at the end of week 48 and every 6 months thereafter in ongoing responders. Please refer to section 4.9 Central Histopathology Review for items required with bone marrow biopsy and aspiration.

[f] MRI (or CT scan) abdomen/pelvis with and without contrast including 3-D spleen and liver volumes will be obtained at screening, at the end of cycle 4, and at the end of cycle 8 or EOT, whichever comes first, and at the time of progressive disease or loss of response (LOR). Interval MRI or CT scans can be performed at the discretion of the investigator. A repeat MRI or CT should be performed at the end of week 48 and every 6 months thereafter in ongoing responders.

[g] A visit on day +30 will be conducted after the EOT visit for follow-up for non-responders. This will be end of study visit (EOS)

[h] After 8 cycles of therapy are completed, labs and visits with the trial site every 6 weeks up to week 48; then every 12 weeks.

[i] Height is to be obtained only at screening.

[j] Long Term Survival: every 6 months after end of study visit until study closure or death of the patient.

4.7 Efficacy Assessments

Efficacy will be determined by overall response based on international consensus response criteria (see Appendix G).

4.7.1 Rules for deriving the variable confirmed overall response

The confirmation response is the next valid consecutive response at least 84 days (12 weeks) from initial response. The time of response is the actual date of response, not the end of cycle which includes the response.

In patients whose response commences in later cycles before the end of cycle 8 (eg, during cycle 6, 7, or 8), the duration of response will be assessed by ongoing laboratory studies and ongoing visits, performed every 6 weeks. Patients who exhibit a response during cycles 1-8 (or during cycles 9-16), but subsequently demonstrate loss of response before cycle 8 is completed (or before cycle 16 is completed for patients being re-treated), such individuals will not be re-treated. Retreatment after cycles 1-8 is only applicable to patients who exhibit an ongoing response at the time of completion of cycle 8.

In case report forms/study e-CRFs, the confirmed response will be denoted by a subscript 'c', whereas initial responses or unconfirmed responses (eg, responses not yet lasting 12 weeks) will display the subcript 'uc'. For example, if a Major response is confirmed at 12 weeks (Table 3 below, column 3), it will be denoted as 'Major Response$_c$' or 'MR$_c$'; whereas an initial Major Response will be denoted as 'Major Response$_{uc}$' or 'MR$_{uc}$'.

Table 3 Acceptable combinations for initial and confirmed response

Initial Response	Response at 12 weeks	Confirmed response level
Major$_{uc}$	Major$_{uc}$	Major$_c$
Major$_{uc}$	Partial$_{uc}$	Partial$_c$
Partial$_{uc}$	Partial$_{uc}$	Partial$_c$
Partial$_{uc}$	Major$_{uc}$	Partial$_c$
CI$_{uc}$	CI$_{uc}$	CI$_c$
CI$_{uc}$		CI$_c$
CI$_{uc}$	Major$_{uc}$	CI$_c$
Partial$_{uc}$	Partial$_{uc}$	CI$_c$
Major$_{uc}$	CI$_{uc}$	CI$_c$
	CI$_{uc}$	

CI: "Clinical Improvement" per international response criteria

4.7.2 Additional aspects to disease evolution

The international consensus response criteria define both progressive disease and loss of response (see Appendix G).

4.8 Safety assessments

Safety assessments will consist of evaluating all adverse events and serious adverse events, laboratory parameters including hematology and chemistry, vital signs, physical examinations, and documentation of all concomitant medications and/or therapies.

4.8.1 Laboratory evaluations

All evaluations must be performed according to the Visit Schedule and Assessment (Table 2). When abnormal laboratory values or test results constitute an adverse event (ie, induces clinical signs/symptoms or requires therapy) they must be recorded on the Adverse Events CRF.

All laboratory values must be drawn and assessed PRIOR to administration of SGN-35 on the day of its administration. Baseline laboratory values need not be repeated if performed within 72 hours of the initial dose of SGN-35.

Vital signs and Physical Examination

A physical examination and vital signs must be performed at baseline, and the beginning of each cycle, and at the end of treatment (EOT), or progressive disease, whichever comes first, and at time of loss of response (LOR). Vital signs and physical exams will also occur on day +30 after EOT which will be end of study visit in non-responders; in responders—vital signs and physical examination will occur every six weeks after completion of 8 cycles of therapy until week 48, then every 12 weeks.

More frequent exams may be performed as clinically indicated. Vital signs include heart rate, blood pressure, and body temperature. Height (in cms) and weight (in kgs) will be captured at baseline and weight (in kgs) will be captured at the beginning of each cycle. ECOG status will be recorded at these visits.

Information about the physical examination must be present in the source documentation at the study site. Significant findings present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after the start of study drug that meets the definition of an adverse event must be recorded on the CRF.

Performance Status

The ECOG Performance Status Scale will be used in this study (Appendix A).

Hematology

Hematology will include total white blood cell count with differential (neutrophil count lymphocyte, monocyte, eosinophil, basophil, mast cell, blast count, and immature granulocytes), hemoglobin, hematocrit, platelet count and reticulocyte count (% and absolute). Hematology labs are required at screening, on day 1 of each cycle during cycles 1 to 8 , day 8 and 15 of cycle 1, day 10 of cycles 2 to 8, at end of treatment (EOT), or time of progressive disease (whichever comes first), and/or at time of loss of response (LOR). Hematology will also be drawn on day +30 after EOT in non-responders; in responders—hematology will be drawn every six weeks after completion of 8 cycles of therapy until week 48, then every 12

weeks. For cycles 9-16, end of treatment cycle 16 and end of study, hematology labs should be repeated exactly as cycle 1-8.

Blood chemistry

Biochemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total and direct bilirubin, albumin, alkaline phosphatase, SGOT and SGPT, LDH, and uric acid, (phosphorus will be additionally done on cycle 1 day 1, cycle 1 day 3 and cycle 1 day 8 only, for complete evaluation of tumor lysis), amylase, and lipase. Blood chemistry labs are required at screening, on day 1 of each cycle during cycles 1 to 8, day 3 of cycle 1 (for complete evaluation of tumor lysis), day 8 of cycle 1, day 15 of cycle 1, at the end of treatment - (EOT) or at time of progressive disease (whichever comes first), and/or at time of loss of response (LOR). Blood chemistry will also be drawn on day +30 after EOT in non-responders; in responders, blood chemistry will be drawn every six weeks after completion of 8 cycles of therapy until week 48, then every 12 weeks. For cycles 9-16, end of treatment cycle 16 and end of study, chemistry labs should be repeated exactly as cycle 1-8. Phosphorus is not to be repeated after cycle 1 day 8.

Coagulation

Coagulation includes PT/INR and PTT. These labs are required on screening, day 1 of each cycle during cycles 1 to 8, and at the end of treatment (EOT) after cycle 8, or progressive disease, whichever comes first. PT/INR and PTT are NOT required for re-staging, at cycles 9-16, end of treatment cycle 16 and end of study.

Serum Tryptase Level

Serum tryptase levels are obtained at screening, day 1 of each cycle, at the end of treatment (EOT), or at time of progressive disease (whichever comes first), and/or at time of loss of response (LOR). Serum tryptase will also be drawn on day +30 after EOT in non-responders; in responders, serum tryptase level will be drawn every six weeks after completion of 8 cycles of therapy until week 48, then every 12 weeks. **If the serum tryptase assay sensitivity does not permit recording of specific values above 200 ng/ml, the sample should be diluted to obtain a specific serum tryptase value rather than a non-specific value of ">200 ng/ml".** For cycles 9-16, end of treatment cycle 16 and end of study, serum tryptase should be repeated exactly as cycle 1-8.

Pregnancy Test

A pregnancy test will be obtained relevant patients during screening, day 1, and on day 1 of each treatment cycle for cycles 1- 8 (patients who need re-treatment will undergo pregnancy testing during re-staging and during potential re-treatment cycles ie, cycles 9-16). Pregnancy test will be done at the end of cycle 8 (end of treatment) and if re-staged, end of treatment cycle 16 and end of study (30 day follow up) visit.

Chest X-Ray (2 views- PA and Lateral)

A chest-x-ray (2 views-PA and lateral) will be performed at screening. If findings considered disease-related are found on chest x-ray at screening (eg, pleural effusion), then a chest x-ray(2 views-PA and lateral) will be performed at the end of cycles 4 and 8 or EOT, whichever comes first, and at the time of progressive disease or loss of response (LOR). A chest X-ray (2 views-PA and lateral) will also be done if patient is assessed for re-staging to get additional

8 cycles of treatment. Interval chest x-rays can be performed at the discretion of the investigator.

Electrocardiogram

An ECG must be performed within 28 days prior to Day 1.

MRI (or CT) Abdomen / Pelvis with and without contrast including 3D spleen and liver volumes

An MRI Abdomen/Pelvis with and without contrast including 3-D spleen and liver volumes (CT with and without contrast including 3-D spleen and liver volumes may be used instead) must be performed within 28 days prior to Day 1 and repeated at the end of cycle 4, and at the end of cycle 8 or EOT, whichever comes first, and at the time of progressive disease. Interval CT scans can be performed at the discretion of the investigator. Repeat MRI (or CT) abdomen/pelvis with and without contrast including 3D spleen and liver volumes will be performed at time of Loss of Response (LOR) through the re-staging studies and repeated during re-treatment cycles 9-16 on a schedule identical to cycles 1 and 2-8.

If patients are removed from study before the end of cycle 4, an MRI (or CT) abdomen / pelvis with and without contrast including 3D spleen and liver volumes should be performed at completion/discontinuation if feasible.

After completion of 8 cycles, a repeat MRI or CT abdomen/pelvis with and without contrast including 3D spleen and liver volumes should be performed at the end of week 48 and every 6 months thereafter in ongoing responders.

Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) Modified for Mast Cell Symptoms (Appendix F)

The MPN-SAF modified for mast cell symptoms will be completed by the patient at screening, day 1 of the trial, day 1 of each cycle through 8 cycles, end of study, and for ongoing responders, every 6 weeks at the time of their maintenance visits through week 48, then every 12 weeks thereafter. The MPN-SAF modified for mast cell symptoms will also be filled out at time of progressive disease or loss of response (LOR). It will also be completed during re-treatment cycles (cycles 9-16) according to the schedule outlined in cycle 1 and 2-8.

Visits, Laboratory Studies and Procedures at Time of Loss of Response (LOR)

At the time of protocol-defined loss of response (LOR) after completion of 8 cycles of therapy, patients will undergo all screening labs (except for PT and PTT and 12-lead EKG) to re-stage disease before re-initiation of SGN-35 for up to an additional 8 cycles (eg, cycles 9-16). For re-treatment during cycles 9-16, the schedule of laboratory studies, exams, and procedures will be identical to cycles 1 and 2-8, with an end of treatment (EOT) visit at the completion of cycle 16 of therapy except PT and PTT which will not be performed with cycles 9-16, end of treatment (EOT) visit at the completion of cycle 16 or end of study.

4.9 Central Histopathology Review

Central histopathology review will be performed in University of New Mexico. This will include review of peripheral blood smear (results of CBC should also be submitted), bone marrow aspirate, bone marrow core biopsy and review of any biopsied tissue with mast cell involvement. The time points for collection of bone marrow aspirate and biopsy material includes the following:

1. Pre-trial (screening); see note in protocol (section 3.3.1) regarding the use of material within 3 months prior to signing study consent:

   If some histopathologic studies for mast cell disease were performed within 3 months prior to signing the consent, such material can be used in place of or to complement histopathologic studies for screening after discussion between Drs. Gotlib, Verstovsek, and George to ensure sufficient quality and quantity of sample for central histopathologic review and testing. However, any histopathologic studies that were not performed should be undertaken during the screening.
2. End of cycle 4
3. End of cycle 8, or at the EOT, whichever comes first
4. At the time of loss of response (LOR) or progressive disease. For patients with LOR, marrows will be performed during the re-staging period and repeated during re-treatment cycles 9-16 on a schedule identical to cycles 1 and 2-8.
5. After completion of 8 cycles, for ongoing responders, a repeat bone marrow aspirate and biopsy should be performed at the end of week 48 and every 6 months thereafter.

Peripheral blood smears and bone marrow aspirates should be unstained or stained with a Wright Giemsa stain. Biopsy slides will be stained with Hematoxylin-Eosin stain. Special stains (ie, reticulin, etc.) and immunohistochemical stains (ie, CD117, tryptase, and CD25, and CD30) will be performed on representative paraffin blocks from biopsies of tissues with mast cell disease (or unstained slides if blocks cannot be provided). Flow cytometry immunophenotyping will be performed on bone marrow (ideal) or peripheral blood (if mast cell leukemia present) for analysis of mast cell phenotype which includes CD117, CD25, CD2, and CD30.

Each institution will perform a *KIT* D816V mutation from bone marrow aspirate (if aspirate not available, then core biopsy material). Institutions may obtain *KIT* mutation status from peripheral blood.

The following are requested by Dr. Tracy George at University of New Mexico for central histopathology review which must be completed before formal drug treatment is started (eg, day 1 infusion). This information will also be provided separately in a lab manual appendix:

1- 2 peripheral blood smears (unstained preferred)

1-3 bone marrow aspirate smears (unstained preferred)

8-10 unstained bone marrow biopsy slides

1 heparinized (green top) tube of bone marrow aspirate (3 ml minimum) for flow cytometry

5 Notable laboratory value criteria, special methods and scales

Performance status scale: ECOG.

Adverse event scale: NCI CTC version 4.03.

6 Data Handling and Record Keeping

6.1 Case Report Forms

Investigator is responsible for entering the information required by the protocol into the Case Report Forms (paper or electronic, that uses validated software and conforms to FDA requirements for electronic data capture). If using electronic Case Report Forms, during system failures data is captured on paper and is later transferred to electronic Case Report Forms. The Investigator must certify that the data are complete and accurate by applying an electronic signature to the electronic Case Report Form and later receives a CD-ROM or paper copies of the patient data for archiving at the investigational site.

All data requested on the CRF must be recorded. All missing data must be explained.

6.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

6.3 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement

with Seattle Genetics. In such an instance, it is the responsibility of the lead investigator (the study sponsor) to inform other investigators/institutions as to when these documents no longer need to be retained.

6.4 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (ie, that the subject is alive) at the end of their scheduled study period.

7 Statistical methods

7.1 Populations

Two populations will be considered for the evaluation of this study:

1. The primary efficacy population includes all patients who have received at least 1 dose of SGN-35.

2. The safety population includes all patients in the study who received at least one dose of SGN-35. The safety population will be used for all safety analyses.

7.2 Background and demographic characteristics

Qualitative background variables (sex, race, stage of disease, etc.) will be summarized using contingency tables. Appropriate descriptive statistics will be used to summarize quantitative background variables (age, weight, etc.). All demographic and disease related data will be listed in detail.

7.3 Study medication

The dosage of SGN-35 of each patient will be listed. In addition, descriptive statistics will be used to summarize the duration of exposure of the study medication, the number of patients by the maximum number of doses received, and the number of patients who experienced dose reduction by duration of exposure. The reasons for dose change of the study medication will also be listed.

7.4 Concomitant therapy

Concomitant medications and significant non-drug therapies prior to and after the start of the study medication will be summarized by dose level according to the Anatomical-Therapeutic Chemical (ATC) classes.

7.5 Primary Objective- Efficacy evaluation

The efficacy of the regimen will be assessed in this study. The primary efficacy endpoint is response rate. A responder is an ASM or mast cell leukemia patient (with or without an AHNMD) who experiences a complete or partial remission, or clinical improvement per international consensus response criteria. Patients with stable disease (SD) or progressive disease (SD) are considered non-responders (NR). Patients with missing tumor assessment or who die or discontinue the study before having their first assessment will be considered non-responders. Best clinical response will be tabulated. The rate of complete remission, partial remission, and clinical improvement (CI) will be estimated and its 95% confidence interval will be provided.

7.6 Secondary Objectives

7.6.1 Safety evaluation

The assessment of safety will be based on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data will be considered as appropriate.

Adverse events will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (eg, severity or relatedness to study medication) will be listed as appropriate.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

7.6.2 Expression of CD30 on neoplastic mast cells

The burden of CD30+ neoplastic mast cells will be determined by immunophenotyping and/or immunohistochemistry and will be compared between pre- and post-SGN-35 treatment samples. Evaluation will be undertaken by central pathology review by Dr. Tracy George at University of New Mexico. Reduction of mast cell burden will also be recorded pre-and post SGN-35 therapy primarily by evaluation of peripheral blood (if mast cell leukemia) and bone marrow aspirate and core biopsy. Change of serum tryptase levels from baseline at the respective assessments will be evaluated as a surrogate marker for histopathologic response.

7.6.3 Myeloproliferative Neoplasm Symptom Assessment Form (MPNSAF) modified for Mast Cell Symptoms

Total symptom score and QOL will be assessed by a modified version of the MPNSAF (modified for mast cell symptoms) by recording mean and median scores with ranges will be recorded pre- and post-treatment with SGN-35 (Appendix F).

7.6.4 Duration of Response (DoR) and Time to Response (TTR)

The duration of (confirmed) overall response (DoR) is defined as the time from the start of the first confirmed response until the date of the first documented and confirmed disease progression or death due to ASM or MCL. The Kaplan-Meier product-limit method will be used to summarize the response duration. If a patient did not progress or die due to ASM or MCL at the time of the analyses, DoR will be censored at the date of the last adequate response assessment.

Time to response (TTR) is defined as the time from the date of start of treatment to the date of first confirmed response. Time to response will be censored at the date of the last adequate response assessment in patients did not progress or die due to any cause and at maximum follow-up date (ie, date of first patient first visit (FPFV) to date of last patient last visit (LPLV) used for the analysis) in patients who progressed or died due to any cause. Kaplan-Meier product-limit estimates will be used to summarize the time to response.

7.6.5 Progression-free survival (PFS) and overall survival

Progression-free survival (PFS) is defined as the time from the date of start of treatment until the date of first documented confirmed disease progression or death or institution of new therapy. If a patient did not progress or die due to any cause at the time of the analyses, PFS will be censored at the date of the last adequate response assessment. Kaplan-Meier product-limit estimates will be used to summarize PFS. For overall survival, patients will be contacted every 6 months until the study closure or death.

7.7 Interim analyses

An interim analysis will be provided after enrolling 11 evaluable patients, as described in Section 7.8.

7.8 Sample size and power considerations

The primary endpoint is response rate per international consensus response criteria (see Appendix G).

The trial will be carried out as a Simon two-stage Optimum design with a total ***potential*** sample size of 26 patients (Simon R, 1989). The first stage will be this investigator-initiated phase II study of 11 patients. We assume that the probability of accepting the treatment when the true response rate is $\leq$ 10% is less than or equal to 10%, and the probability of rejecting the treatment when the true response rate is $\geq$ 30% is less than or equal to 15%.

Under these assumptions, the stopping rules are as follows: Accrue a cohort of 11 patients in this first stage phase II study. If 2 or more patients out of 11 respond, the study will be amended to enroll an additional 15 patients in the second stage. If less than 2 responses are seen, the study will be halted. At the end of the second stage, if 5 or more patients out of 26 respond, the regimen will be considered for further investigation in the treatment of advanced mastocytosis. With this design, the chance of falsely claiming that regimen is efficacious (alpha) is 8.7%, and the power is 85%. The probability of stopping early is 70% under the null hypothesis of a 10% response rate is 10%; it is 11% if the true response rate is 30%.

8 Procedures and instructions

8.1 Special safety-related procedures

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or

intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; eg, change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and entered on the appropriate case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.1.1 Instructions for rapid notification of Serious Adverse Events

Reporting responsibility

For all studies for which Seattle Genetics has provided Product:

• **Reporting Timeframe:** The Principal Investigator (Stanford) will report to Seattle Genetics Drug Safety by facsimile any Serious Adverse Event (SAE) that occurs in a study subject within 24 hours
of first awareness of the event. The Co-Principal Investigator from the sub-site will report any SAEs to the main site (Stanford) within 24 hours by facsimile or by email to hkaur@stanford.edu and these will be submitted to Seattle Genetics Drug Safety by Principal Investigator.

• **Reporting Forms:** The Principal Investigator and Co-Principal Investigator will report such SAEs using the Seattle Genetics SAE Report Form or the approved local regulatory form (ie, FDA MedWatch form, CIOMS, etc.) *to include an assessment of causality to the Product*. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

• **Reporting Period:** The reportable events that are subject to this provision are those that occur from the start of administration of the first dose of the Product through thirty (30) days after discontinuation of the Product. SAEs occurring more than thirty (30) days after discontinuation of the Product that are assessed by the Investigator as related to the Product should also be reported.

• **Follow-up Information:** The Principal Investigator will assist Seattle Genetics in investigating any SAE and will provide any follow-up information reasonably requested by Seattle Genetics.

• **Regulatory Reporting:** Reporting an SAE to Seattle Genetics does not relieve the Principal Investigator conducting the study of the responsibility for reporting it to the FDA, local regulatory authority, or IRB/IEC as required.

Sponsor Responsibilities

As the sponsor of the study, the Principal Investigator and/or Institution must ensure that the study is conducted in accordance with the provisions of the ICH GCP Guidelines and all applicable local and regulatory requirements. The Principle Investigator must assume all regulatory responsibilities including, but not limited to, IRB/IEC approvals, regulatory approvals, monitoring responsibilities and any and all reporting obligations to local regulatory Authorities.

EC/IRB Notification by Investigator

Reports of all serious adverse events (including follow-up information) must be submitted to the EC/IRB in accordance with the institutional policy. Copies of each report and documentation of EC/IRB notification and receipt will be kept in the Study binder.

8.1.2 Instructions for rapid notification of pregnancies

Each pregnancy that started during the study must be reported by the investigator to Seattle Genetics within 24 hours of learning of its occurrence. Pregnancies and pregnancy follow-up should be reported on the Clinical Trial Pregnancy Form but any serious adverse event experienced during pregnancy must be reported on the FDA Form 3500 and Serious Adverse Event Report Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications and their relation to the Seattle Genetics study drug (or therapy).

8.2 Administrative procedures

8.2.1 Changes to the protocol

Study Initiation

As the sponsor of the study, the Principal Investigator and/or Institution must provide the following to Seattle Genetics prior to initiation of Seattle Genetics support (provision of Product):

• Final study protocol

• Fully executed IST Agreement
• Regulatory Response Documentation (IND or CTA documentation if applicable)
• IRB/IEC approval

Study Maintenance

Throughout the study, Seattle Genetics requires the following:
• At least one safety study status update per year, to include information on enrollment and study completion dates.
• Notification of any amendment to the original protocol after the research has begun; and *immediate* notification of any amendments made due to safety reasons.

Study Closure

Any Investigator and/or Institution conducting an IST is contractually required to provide Seattle Genetics with a written report of the final study results and a copy of the IND Annual Report (or equivalent in rest of world regions). Upon study closure, the Investigator and/or Institution will be required to certify that all safety reporting obligations were met.

8.2.2 Monitoring procedures

The Lead study investigator (Study Sponsor) is responsible for reviewing the protocol and case report forms with the investigators and their staff prior to study. The responsibilities of the Sponsor (or designee) include project compliance, data abstraction, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team and study-level medical monitoring. Accrual rates and extent and accuracy of evaluations and follow-up are to be monitored periodically throughout the study period. Potential problems will be brought to the attention of the study team for discussion and action.

Investigators are responsible for the completeness of patient records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and also to ensure that study medication is being stored, dispensed and accounted for according to specifications. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of serious adverse events and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the case report forms are performed according to the institutional and regulatory guidelines.

It is the responsibility of the Principal Investigator at each of the study centers to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record. Random-sample data quality and protocol compliance audits will be conducted by the Sponsor (or designee) remotely (fax) or in person to check the completeness of patient records, the accuracy of entries on the case report forms, the adherence to the protocol and to Good Clinical Practice. The investigator must give the monitor access to relevant hospital or clinical records, to confirm their

consistency with the case report form entries. No information in these records about the identity of the subjects will leave the study center.

8.2.3 Auditing procedures

A regulatory authority may wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform Seattle Genetics immediately that this request has been made.

Seattle Genetics Good Clinical Practice Quality Assurance Unit may request to conduct an audit of clinical research activities to evaluate compliance with the principles of Good Clinical Practice.

8.2.4 Handling of study medication

All study medication will be supplied to the principal investigator by Seattle Genetics. Drug supplies must be kept in an appropriate, secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger, a copy of which must be given to Seattle Genetics at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels, or any partly-used or unused drug supply. At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused drug containers, drug labels and a copy of the completed drug disposition form to Seattle Genetics.

8.2.5 Disclosure and confidentiality

By signing the protocol, the investigator agrees to keep all information provided by Seattle Genetics in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Seattle Genetics (eg, investigators' brochures, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Seattle Genetics to the investigator may not be disclosed to others without direct written authorization from Seattle Genetics, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

8.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).
The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

8.3.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Seattle Genetics before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Seattle Genetics. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

8.3.2 Informed consent

Patients will be required to sign a statement of informed consent which meets the requirements of the code of Federal Regulations (Federal Register Vol. 46, No. 17, Jan. 27, 1981, part 50) and the IRB of this center. The medical record should include a statement that written informed consent was obtained (and document in the record the date written consent was obtained before) and the patient is enrolled in the study.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

Consent Process

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The discussion will review the alternatives available, why the risks are reasonable in relation to the anticipated benefits, incentives, costs that will or may be incurred as a result of participation in the study, as will the efforts to maintain the confidentiality will also be discussed.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

A copy of the signed original consent form will be given to the patient.

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APPENDIX A
Performance Status Criteria

ECOG Performance Status Scale		Karnovsky 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 (eg, light housework, office work).	**80**	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	**60**	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	**40**	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	**20**	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	**0**	Dead.

APPENDIX B

Criteria to Diagnose Systemic Mastocytosis (SM Criteria)

Major criterion	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria	a. >25% of all mast cells are atypical cells (type I or type II) On bone marrow smears or are spindle-shaped in mast cell Infiltrates detected on sections of visceral organs
	b. c-kit point mutation at codon 816 in the bone marrow or another extracutaneous organ
	c. Mast cells in bone marrow or blood or another extracutaneous organ express CD2 or/and CD25
	d. Baseline serum tryptase concentration > 20 ng/ml (in the case of an unrelated myeloid neoplasm, (d) is not valid as an SM criterion)

If at least one major and one minor or three minor criteria are fulfilled, then the diagnosis is systemic Mastocytosis=SM.

APPENDIX C

Diagnostic Criteria for Aggressive Systemic Mastocytosis and Mast Cell Leukemia

Aggressive Systemic Mastocytosis

Meets criteria for SM

One or more “C” findings

No associated clonal hematologic malignancy/disorder (AHNMD)*

No evidence of mast cell leukemia

*Patients with aggressive systemic mastocytosis who also are found to have an AHNMD are eligible for this protocol

Mast Cell Leukemia

Meets criteria for SM

Biopsy shows a diffuse infiltration, usually interstitial pattern, by atypical, immature mast cells

Bone marrow aspirate smears show 20% or more mast cells

Mast cells account for 10% or more of peripheral blood white cells

NOTE: Patients may also be enrolled if mast cells account for <10% of the peripheral blood white blood cells; such patients are considered to be in the pre-phase of mast cell leukemia and are referred to as “aleukemic mast cell leukemia.”

APPENDIX D
Mediator Drugs to Ameliorate Symptoms Related to Systemic Mastocytosis*

Symptom	Step	Drug(s) to be considered
Pruritis, flushing	1	H1 + H2-histamine receptor antagonists
	2	Ketotifen, topical glucocorticoids
	3	PUVA
Cardiovascular symptoms	1	H1 + H2-histamine receptor antagonists
Recurrent hypotension and tachycardia	2	Glucocorticoids**
	3	Aspirin (in selected cases)
Recurrent shock 1		H1 + H2-histamine receptor antagonists + epinephrine on demand (self injected)
	2	Oral glucocorticoids** + epinephrine on demand (self injected)
	3	Aspirin (in selected cases) + epinephrine on demand
GI tract		
Peptic ulcer disease	1	H2-histamine receptor antagonists
	2	Proton-pump inhibitors + H2 blockers
Diarrhea, abdominal pain, cramping, nausea/vomiting	1	H1 + H2-histamine receptor antagonists
	2	Oral cromolyn sodium
	3	Consider trial with leukotriene antagonists
	4	Short-term glucocorticoids**
Skeletal system		
Bone pain	1	Analgesias, aspirin-like drugs (if tolerable) Also consider radiation for severe pain
Osteopenia, diffuse osteoporosis	1	Vitamin D + calcium or estrogen/ testosterone on demand
	2	Bisphosphonates
Neurologic symptoms	1	H1 + H2-histamine receptor antagonists
	2	Oral cromolyn sodium

*From Valent *et al.* Br J Haematol. 2003; 122: 695-717.

APPENDIX E
List of CYP3A Inhibitors and Inducers

CYP3A4/5 Inhibitors

Amiodarone	Diethyldithiocarbamate	Grapefruit juice	Norfloxacin	Sertindole
Anastrozole	Diltiazem	Indinavir	Omeprazole	Sertraline
Azithromycin	Dirithromycin	Isoniazid	Oxiconazole	Troglitazone
Cannabinoids	Disulfiram	Itraconazole	Paroxetine	Troleandomyci
Cimetidine	Entacapone	Ketoconazole	Propoxyphene	Valproic Acid
Clarithromycin	Erythromycin	Metronidazole	Quinidine	Verapamil
Clotrimazole	Ethinyl estradiol	Miconazole	Quinine	Zafirlukast
Cyclosporine	Fluconazole	Nefazodone	Quinupristin	Zileuton
Danazol	Fluoxetine	Nelfinavir	Ranitidine	
Delavirdine	Fluvoxamine	Nevirapine	Ritonavir	
Dexamethasone	Gestodene	Norfluoxetine	Saquinavir	

CYP3A4/5 Inducers

Carbamazepine	Nafcillin	Phenylbutazone	Rifampin	Troglitazone
Dexamethasone	Nelfinavir	Phenytoin	Rofecoxib (mild)	
Ethosuximide	Nevirapine	Primidone	St. John’s wort	
Glucocorticoids	Oxcarbazepine	Progesterone	Sulfadimidine	
Griseofulvin	Phenobarbital	Rifabutin	Sulfinpyrazone	

APPENDIX F

Myeloproliferative Neoplasm Symptom Assesment Form with Mast Cell Disorder Symptoms
MPN-SAF (MCD)

Instructions: Please fill out all questions, as best able, reflecting how these symptoms affected you over the **LAST WEEK** unless directed otherwise. Use a scale of 0 to 10, marking "0" if the symptom is absent, "1" being most favorable, and "10" being least favorable.

Please rate your fatigue (weariness, tiredness) by marking the one number that best describes your fatigue right NOW.	(No fatigue)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Please rate your fatigue (weariness, tiredness) by marking the one number that best describes your USUAL level of fatigue during the past 24 hours.	(No fatigue)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Please rate your fatigue (weariness, tiredness) by marking the one number that best describes your WORST level of fatigue during the past 24 hours.	(No fatigue)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)

Mark the one number that describes how, during the past 24 hours, fatigue has interfered with your:

General activity	(Does not interfere)	0	1	2	3	4	5	6	7	8	9	10	(Completely interferes)
Mood	(Does not interfere)	0	1	2	3	4	5	6	7	8	9	10	(Completely interferes)
Walking ability	(Does not interfere)	0	1	2	3	4	5	6	7	8	9	10	(Completely interferes)
Normal work (includes work both outside the home and daily chores)	(Does not interfere)	0	1	2	3	4	5	6	7	8	9	10	(Completely interferes)
Relations with other people	(Does not interfere)	0	1	2	3	4	5	6	7	8	9	10	(Completely interferes)
Enjoyment of life	(Does not interfere)	0	1	2	3	4	5	6	7	8	9	10	(Completely interferes)

Please continue on reverse side

Myeloproliferative Neoplasm Symptom Assesment Form with Mast Cell Disorder Symptoms
MPN-SAF (MCD)

Mark the one number that describes how, over the LAST WEEK, the following symptoms have affected you.
Use a scale of 0 to 10, marking "0" if the symptom is absent, "1" being most favorable, and "10" being least favorable.

Filling up quickly when you eat (Early Satiety)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Abdominal pain	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Abdominal discomfort	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Inactivity	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Problems with headaches	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Problems with concentration - compared to prior to my SM	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Dizziness/vertigo/lightheadedness	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Numbness/tingling (in your hands and feet)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Difficulty sleeping	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Depression or sad mood	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Problems with sexual desire or function	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Cough	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Night sweats	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Itching (pruritus)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Fever (greater than 100 F/37.8 C)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Unintentional weight loss last 6 months	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Flushing	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Feeling anxious	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Feeling faint or about to pass out (without actually losing consciousness)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Throat or airway swelling or tightening	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Burning sensation in your throat or abdomen	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Fear of your next episode of severe symptoms (anaphylaxis)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Diarrhea	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Intensity of skin lesions (if skin lesions not present, mark "0")	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
Anaphylactic episodes (loss of consciousness)	(Absent)	0	1	2	3	4	5	6	7	8	9	10	(Worst imaginable)
What is your overall Quality of Life?	(As good as it can be)	0	1	2	3	4	5	6	7	8	9	10	(As bad as it can be)

Thank you for your time!

APPENDIX G:

Table 3. Organ damage in patients with advanced SM: eligibility and response criteria for CI

Organ damage	Organ damage eligible for CI response	CI response criteria
Nonhematologic		
Ascites or pleural effusions	(1) Symptomatic ascites or pleural effusion requiring medical intervention such as use of diuretics (grade 2), OR (2) ≥ 2 therapeutic paracenteses or thoracenteses at least 28 d apart over 12 wk prior to study entry (grade 3), and one of the procedures is performed during the 6 wk prior to drug start	(1) Complete resolution of symptomatic ascites or pleural effusion* AND no longer in need of diuretic(s) for ≥ 12 wk, OR (2) No therapeutic paracentesis or thoracentesis for ≥ 12 wk
Liver function abnormalities	≥ Grade 2 abnormalities in direct bilirubin, AST, ALT, or AP† in the presence of ascites, and/or clinically-relevant portal hypertension, and/or liver MC infiltration that is biopsy-proven or other causes for abnormal liver function are not identified	Reversion of 1 or more liver function tests to normal range for ≥ 12 wk
Hypoalbuminemia	≥ Grade 2 hypoalbuminemia (< 3.0 g/dL)	Reversion of albumin to normal range for ≥ 12 wk
Symptomatic marked splenomegaly	Symptomatic marked splenomegaly: a spleen that is palpable > 5 cm below the left costal margin and the patient endorses symptoms of discomfort and /or early satiety	≥ 50% reduction in palpable splenomegaly and no endorsement of discomfort and/or early satiety for ≥ 12 wk (3D computed tomography/magnetic resonance imaging evaluation may also be undertaken.)
Hematologic		
ANC	Baseline grade ≥ 3 ANC (< 1×10^9/L)	A minimum 100% increase in the ANC and an ANC of at least 0.5×10^9/L for ≥ 12 wk
Anemia (transfusion-independent)	Grade ≥ 2 anemia (Hb < 10 g/dL)	An increase in Hb level of at least 2 g/dL that is maintained for ≥ 12 wk
Anemia (transfusion-dependent)	Transfusion of a minimum of 6 units of PRBC in the 12 wk before the start of treatment with the most recent transfusion occurring in the previous 4 wk. RBC transfusions are only considered as part of the baseline criteria if they are administered for an Hb level ≤ 8.5 g/dL and not associated with bleeding, hemolysis, or therapy	Transfusion independence for ≥ 12 wk and maintenance of a minimal Hb level of 8.5 g/dL at the end of the 12 wk period of response duration
Thrombocytopenia (transfusion-independent)	Grade ≥ 2 thrombocytopenia (< 75×10^9/L)	A minimum 100% increase in the platelet count and an absolute platelet count increase of at least 50×10^9/L and no need for platelet transfusions for ≥ 12 wk
Thrombocytopenia (transfusion-dependent)	1) Transfusion of a minimum of 6 units of apheresed platelets during the 12 wk preceding treatment; and 2) at least 2 units transfused in the previous 4 wk; and 3) transfusions are administered only for a platelet count < 20×10^9/L	Transfusion-independence for a minimal period of 12 wk and maintenance of a platelet count of ≥ 20×10^9/L

The response criteria were determined using National Institutes of Health CTC version 4.03.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; PRBC, packed red blood cells.

*Radiologic use of the term *trace* or *minimal* for ascites or pleural effusion indicates a substantial improvement of pretreatment pathologic fluid accumulation, which required medical intervention. These terms are acceptable in the absence of the radiologists' use of the term(s) *complete disappearance* or *resolution* to describe the change in ascites or effusion.

†Gamma-glutamyl transferase can be used to determine the liver vs bone origin of alkaline phosphatase but is not considered eligible as a liver-related organ damage laboratory abnormality. The grades and associated laboratory ranges above the upper limit of normal used for the total bilirubin according to CTC version 4.03 should be applied to the direct bilirubin.

RESPONSE CRITERIA **APPENDIX G Contd.:**

APPENDIX G: WG-MRT-ECNM consensus response criteria for patients with ASM, MCL, and SM associated with a myeloid neoplasm

Complete remission (CR)*
Requires all 4 criteria and response duration must be ≥ 12 wk
No presence of compact neoplastic mast cell aggregates in the BM or other biopsied extracutaneous organ
Serum tryptase level < 20 ng/mL†
Peripheral blood count remission defined as ANC ≥ 1×10^9/L with normal differential, Hb level ≥ 11 g/dL, and platelet count ≥ 100×10^9/L
Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (CI findings)‡
Partial remission (PR)*
Requires all 3 criteria and response duration must be ≥ 12 wk, in the absence of both CR and progressive disease (PD)
Reduction by ≥ 50% in neoplastic MCs in the marrow and/or or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage
Reduction of serum tryptase level by ≥ 50%†
Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (CI finding(s)) ‡
Clinical improvement (CI)*
Response duration must be ≥ 12 wk
Requires 1 or more of the nonhematologic and/or hematologic response criteria to be fulfilled (see Table 3) in the absence of both CR/PR assignment or progressive disease (PD)
Stable disease (SD)
Not meeting criteria for CR, PR, CI, or PD
Progressive disease (PD)§
Requires at least 1 element of either criteria 1 or 2 and duration must be ≥ 8 wk
(1) For patients with baseline grade 2 nonhematologic organ damage: a) worsening by 1 grade, AND b) minimum 100% increase (doubling) of laboratory abnormality.
For patients with baseline ≥ grade 2 albumin: (a) worsening by 1 grade, AND (b) decrease by ≥ 0.5 g/dL.
For patients with baseline ≥ grade 3 nonhematologic organ damage: minimum 100% increase (doubling) of laboratory abnormality.
For patients with baseline ≥ grade 2 transfusion-independent anemia or thrombocytopenia: New transfusion dependence of ≥ 4 units of RBCs or platelets at 8 wk.
For patients with baseline transfusion-dependent anemia or thrombocytopenia: ≥100% increase in the average transfusion frequency for an 8-wk period compared with the 12-wk pretreatment period
For patients with baseline grade ≥ grade 3 neutropenia: (a) > 50% decrease in neutrophil count, AND (b) absolute decrease of neutrophil count of ≥ 250/mm^3, AND c) grade 4
(2) Development of at least 10-cm palpable symptomatic splenomegaly for a baseline spleen size of not palpable or ≤ 5 cm, OR if baseline symptomatic splenomegaly is > 5 cm, a > 50% worsening and development of at least 10 cm of palpable symptomatic splenomegaly compared with the baseline value.¶
Loss of response (LOR)
Loss of a documented CR, PR, or CI that must be for ≥8 wk. Downgrading of CR to PR or PR to CI is considered as such but is not considered as loss of response unless CI is also lost for a minimum of 8 wk. The baseline value for LOR is the pretreatment measurement(s) and not the nadir values during response.

Guidelines for adjudicating response are as follows: (1) Only disease-related ≥ grade 2 organ damage is evaluable as a primary endpoint in clinical trials. (2) Response adjudications of CR, PR, SD, PD, and LOR should only be applied to these ≥ grade 2 organ damage findings in the context of trials. (3) Disease status at the time of patient removal from the study singularly relates to the updated status of initial ≥ grade 2 organ damage finding(s). (4) Exclusion of drug-related toxicity and/or other clinical issues (eg, gastrointestinal tract bleeding in the case of worsening anemia/transfusion-dependence) should be undertaken before assigning the designation PD or LOR in a patient with worsening of baseline ≥ grade 2 organ damage.

*Responses that are not maintained or confirmed for a period of at least 12 wk do not fulfill criteria for CR, PR, or CI; however, both maintained and unmaintained (< 12-wk duration) responses in organ damage should be recorded to determine median duration of response.

†Only valid as a response criterion if the pretreatment serum tryptase level is ≥ 40 ng/mL.

‡Biopsy of organ(s) in addition to the BM to evaluate for SM-related organ damage may be considered.

§Preservation of at least one CI finding permits a patient to maintain the response of 'CI' if 1 or more CI findings are lost but none meet criteria for progressive disease (PD). However, if 1 or more of the CI findings become PD, then the CI finding assignment is lost and the patient meets criteria for PD. The baseline value for evaluating PD is the pretreatment measurement(s). The PD findings must be considered related to the underlying disease and not to other clinical factors. Progression of an underlying chronic myeloid neoplasm to AML is also considered PD in the setting of clinical trials.

¶For clinical trials using 3D computed tomography or magnetic resonance imaging as an additional modality to quantify organomegaly, progression in splenomegaly is defined as an increase in spleen volume of at least 25%.