Systemic mastocytosis (SM) is characterized by accumulation of neoplastic mast cells and is classified into indolent and aggressive forms. The latter include aggressive SM (ASM), mast cell leukemia (MCL), and SM associated with a myeloid neoplasm wherein 1 or both disease compartments exhibit advanced features. These variants, henceforth collectively referred to as advanced SM for the purposes of this report, are typically characterized by organ damage and shortened survival duration. In contrast to indolent SM, in which symptoms are usually managed by noncyto-toxic antimediator therapy, cytoreduction is usually necessary for disease control in advanced SM. Unfortunately, current drug treatment of these patients rarely results in complete clinical and histopathologic remissions or improved survival time. Previously defined response criteria were adapted to the heterogeneous presentations of advanced SM and the limited effects of available drugs. However, recent advances in understanding the molecular pathogenesis of SM and the corresponding prospect in targeted therapy make it a priority to modify these criteria. Our current study is the product of an international group of experts and summarizes the challenges in accomplishing this task and forwards a new proposal for response criteria, which builds on prior proposals and should facilitate response evaluation in clinical trials. (Blood. 2013;121(13):2393-2401)

Introduction

A combination of clinical, morphologic, immunophenotypic, and molecular analyses are required to establish a diagnosis of systemic mastocytosis (SM) according to World Health Organization (WHO) criteria (Table 1).1-3 In current consensus classification proposals, SM variants are partly distinguished by the presence of clinico-pathologic criteria referred to as B finding(s) (> 30% bone marrow [BM] mast cells [MCs] on biopsy and/or serum tryptase levels > 200 ng/mL; increased marrow cellularity/dysplasia without meeting diagnostic criteria for another myeloid neoplasm; or enlargement of liver, spleen, or lymph nodes without evidence of organ damage) and C finding(s) (evidence of organ damage caused by a local MC infiltrate, such as abnormal liver function and/or ascites, hypersplenism, cytopenias, large osteolytic lesions/fractures, and malabsorption with weight loss caused by MC infiltration in the gastrointestinal tract) (Table 2).1-2,4

Indolent SM (ISM) is defined by the absence of C findings. Smoldering SM is a subtype of ISM that displays 2 or more B findings.2 Notwithstanding the morbid burdens imposed on patients by ISM, and the potential of ISM to become more advanced with time, our use of the descriptive term advanced SM herein specifically refers to aggressive SM (ASM), mast cell leukemia (MCL), and “SM with an associated myeloid neoplasm.” The latter term constitutes more than 90% of cases that have been broadly referred to as SM with an associated hematologic non–mast-cell lineage disorder (SM-AHNMD).2 In these patients, the SM and/or the myeloid neoplasm can be relatively indolent or aggressive, but 1 or both disease subsets ultimately contribute to organ damage.

ASM and MCL are characterized by organ damage and WHO-defined histopathologic findings. Specifically, ASM is characterized by multifocal BM infiltration by atypical, often immature MCs with marked fibrosis, and mutation analysis is almost always positive for KIT D816V.2 In MCL, MCs account for more than 20% of nucleated cells on the BM aspirate smears and form a diffuse, compact infiltrate on the core biopsy with usually low levels of fibrosis. In MCL, circulating MCs (> 10% of nucleated cells) may be found; however, in our experience, the aleukemic MCL variant (< 10% MCs in the peripheral blood) is more prevalent.2 A proportion of MCL cases do not exhibit the KIT D816V mutation.
Although uncommon, MCL can present without overt organ damage, but this usually develops within a short period.

Myeloid neoplasms associated with SM include myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), MDS/MPN overlap disorders (eg, chronic myelomonocytic leukemia [CMML]), eosinophilic disorders (eg, chronic eosinophilic leukemia), or acute myeloid leukemia (AML).1,2 Lymphoid neoplasms have also been described in patients with SM, but at much lower frequency. Evaluation of organ damage in SM with an associated myeloid neoplasm might require a tissue biopsy to ascertain the relationship between organ damage and the burden of MC infiltration or myeloid disease.3,5 However, such intervention is often not possible and is not required in all patients.

Response evaluation relies on combined clinical and pathology expertise at the time of both diagnosis and response adjudication. BM MC burden is best quantified by morphologic analysis and immunohistochemical stains such as tryptase, CD117 (KIT), and CD25 on the core biopsy.2 Multiparameter flow cytometric analysis of the BM aspirate (available at some centers with mastocytosis expertise) can also be used to quantify the percentage of MCs, and generally correlates with SM burden by morphologic/immunohistochemical evaluation.6 A thorough cytologic evaluation of the BM smear is also important because dysplasia may be recorded, and most germane, the diagnosis of MCL is based on the number of atypical MCs in BM smears. An increased percentage of MCs in BM aspirate smears and multilineage involvement of the KIT D816V mutation have been correlated with a worse prognosis in SM.7 In patients with SM, eosinophilia has been associated with worse outcomes or has been found to be prognostically neutral.8,9

Recently, CD30 (Ki-1), a cytoplastic and membrane-bound antigen, was identified as a possible immunohistochemical marker of distinction between advanced and indolent forms of SM.10 However, the value of CD30 in distinguishing different subtypes of SM remains uncertain because another study could also detect CD30 by immunohistochemistry in ISM cases.11 Total serum tryptase levels generally reflect the increased burden of MCs in patients with all types of SM. Although discordances can exist between the serum tryptase level and the degree of MC infiltration of the marrow and other organs, it is the most useful and widely available blood marker to assess changes in the MC burden in response to cytoreductive therapy.12

Molecular determination of the KIT mutation status, obtained from either the BM aspirate or biopsy (collected in the preservative formalin with EDTA decalcification to avoid DNA degradation), or from the peripheral blood in MCL or SM with an associated myeloid neoplasm, is a critical part of the WHO diagnosis of SM and fundamentally drives treatment decisions.1,4 Information regarding the KIT mutation status is particularly important in the current era of tyrosine kinase inhibitor therapy because most patients with SM (> 80% in clinical series; 90%-100% in research studies using purified MCs) carry KIT D816V (or, infrequently, D816Y/H).13,14

Table 1. World Health Organization diagnostic criteria for systemic mastocytosis

<table>
<thead>
<tr>
<th>Major criterion</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifocal dense infiltrates of MCs (&gt; 15 MCs in aggregates) are detected in sections of BM and/or other extracutaneous organ(s).</td>
<td>In biopsy sections of BM or other extracutaneous organs, &gt; 25% of the MCs in the infiltrate are spindle shaped; have atypical morphologic features; or, of all MCs in BM aspirate smears, &gt; 25% are immature or atypical.</td>
</tr>
<tr>
<td>Detection of an activating point mutation at codon 816 in KIT in BM, blood, or another extracutaneous organ</td>
<td>MCs in BM, blood, or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.</td>
</tr>
<tr>
<td>Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).</td>
<td></td>
</tr>
</tbody>
</table>

The diagnosis of SM requires at least 1 major criterion and 1 minor criterion or at least 3 minor criteria.

Table 2. Major variants of systemic mastocytosis and B and C findings

<table>
<thead>
<tr>
<th>ISM</th>
<th>Meets criteria for SM. No C findings and no evidence of an AHNMD. The mast cell burden is low, and skin lesions are frequently present.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Bone marrow mastocytosis: ISM with BM involvement, but no skin lesions</td>
<td></td>
</tr>
<tr>
<td>b. Smoldering SM: ISM, but with 2 or more B findings, but no C findings. Usually with skin lesions</td>
<td></td>
</tr>
<tr>
<td>SM-AHNMD*</td>
<td>Meets criteria for SM and criteria for an AHNMD (MDS, MPN, MDS/MPN, AML, or other WHO-defined myeloid hematologic neoplasm, with or without skin lesions).</td>
</tr>
<tr>
<td>ASM</td>
<td>Meets criteria for SM. One or more C findings. No evidence of mast cell leukemia. Variable involvement by skin lesions.</td>
</tr>
<tr>
<td>MCL</td>
<td>Meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature MCs. Bone marrow aspirate smears show 20% or more MCs. Typical MCL: MC comprise 10% or more of peripheral blood white cells. A leukemic MCL: &lt; 10% of peripheral blood white cells are MCs. Usually without skin lesions.</td>
</tr>
</tbody>
</table>

**B findings**

- Bone marrow biopsy showing > 30% infiltration by MCs (focal, dense aggregates) and serum total tryptase level > 200 ng/mL.
- Signs of dysplasia or myeloproliferation, in non-mast-cell lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or only slightly abnormal blood counts.

**C findings**

- Bone marrow dysfunction manifested by 1 or more cytopenia (ANC < 1 × 10^9/L, Hb < 10 g/dl, or platelets < 100 × 10^9/L).
- Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension.
- Skeletal involvement with large osteolytic lesions and/or pathologic fractures.
- Palpable splenomegaly with hypersplenism.
- Malabsorption with weight loss from gastrointestinal tract mast cell infiltrates.

*Headnotes and footnotes added for clarity.

1. A lymphoproliferative disorder or plasma cell dyscrasia may rarely be diagnosed with SM.
2. Must be attributable to the MC infiltrate.
which is an imatinib-resistant mutation.\textsuperscript{15,16} However, such patients may respond to second-generation tyrosine kinase inhibitors such as midostaurin\textsuperscript{17–19} but less likely to nilotinib\textsuperscript{18} or dasatinib, which may, in part, be the result of the short half-life of the drug.\textsuperscript{19,20} Conversely, the rare patients with SM who exhibit a juxtamembrane domain KIT mutation are likely to respond to imatinib\textsuperscript{21} or masitinib.\textsuperscript{22,23}

\section*{Prior response criteria for advanced SM}

Response criteria for advanced SM were first published in 2003 (supplemental Table 1)\textsuperscript{24} and were reiterated in a consensus conference report in 2007.\textsuperscript{4} In this system, evaluation of clinical evidence of organ damage, or C findings, was the foundation for distinguishing levels of response, whereas changes in BM MC burden, serum tryptase level, and organomegaly were additionally used to subclassify levels of major response (MR). These original criteria, or their modified version, have been used to adjudicate responses in case reports or trials of novel agents, including midostaurin,\textsuperscript{17–19} dasatinib,\textsuperscript{19,20,26} masitinib,\textsuperscript{22,23} denileukin diftitox,\textsuperscript{27} RAD001,\textsuperscript{28} daclizumab,\textsuperscript{29} lenalidomide,\textsuperscript{30} thalidomide,\textsuperscript{31} interferon-alpha (with or without corticosteroids),\textsuperscript{32–37} 2-chlorodeoxyadenosine (2-CdA),\textsuperscript{37–43} imatinib,\textsuperscript{38,44,45} and hydroxyurea.\textsuperscript{37}

According to prior consensus response criteria,\textsuperscript{24} MR is defined as normalization of 1 or more C findings. In turn, MR is divided into 3 subcategories: (1) complete remission (resolution of abnormal MC infiltrates in organs, decrease of serum tryptase levels to less than 20 ng/mL, and disappearance of SM-associated organomegaly), (2) incomplete remission (decrease of MC infiltrates and/or serum tryptase levels, and/or visible regression of organomegaly by > 50%), and (3) pure clinical response (without decrease of MC infiltrates, serum tryptase levels, or organomegaly). A partial response (PR) is defined as incomplete regression of 1 or more C findings (good partial response, GPR; > 50% regression of \( \geq 1 \) C findings; and minor response, < 50% regression). Progression of 1 or more C findings, even in the presence of an improvement of other C findings, defines progressive disease (PD). However, specific criteria for what constitutes PD have not been well detailed, except that some trials have used a 50% worsening of 1 or more C findings from baseline.

The Mayo Clinic subsequently published revised response criteria (supplemental Table 2), which are based on 4 levels of adjudication: (1) disease-related symptoms, (2) organomegaly/lymphadenopathy, (3) organ damage (referred to as organopathy), and (4) BM findings.\textsuperscript{47} Levels of response (complete response, major response, partial response and PD) are based on 1 or more of these 4 criteria being met. The Mayo criteria establish minimal baseline laboratory abnormalities for organ damage to be evaluated in an attempt to make responses more clinically relevant.

\section*{Defining nonhematologic and hematologic organ damage: prior challenges and proposed solutions}

There are many shortcomings regarding published SM response criteria. First, achievement of an MR (defined as normalization of \( \geq 1 \) C findings) is permitted in patients with baseline laboratory values just outside of the normal reference range.\textsuperscript{4,24} Second, responses in C findings such as ascites, weight loss, and bone lesions are notoriously difficult to quantify. Third, criteria for baseline red blood cell (RBC) and platelet transfusion dependence and response have not been codified.\textsuperscript{4,24,48} Lastly, the required minimal duration of response is not clearly defined, although a minimal response duration of 8 weeks has been incorporated ad hoc into several trials. Hereafter, we highlight the challenges of defining specific nonhematologic and hematologic organ damage related to advanced MC neoplasms to generate practical and clinically meaningful response criteria that can be adopted across clinical trials.

For these consensus criteria, we use the term organ damage in lieu of C findings. In the following sections and in Table 3, we delineate the criteria for evaluable nonhematologic and hematologic organ damage in advanced SM and define the basis for response (eg, clinical improvement, CI).

\section*{Nonhematologic organ damage}

\subsection*{Ascites}

The development of ascites in SM usually reflects aggressive liver disease and may be accompanied not only by hepatomegaly but also by abnormal liver function test results and/or portal hypertension. More uncommonly, ascites may develop without evidence for hepatopathy, or in conjunction with massive abdominal lymphadenopathy. In prior response criteria, MR is defined as “no ascites” and GPR as a more than 50% decrease in the frequency of paracenteses.\textsuperscript{4,24} These criteria do not take into account the baseline volume of ascites nor the frequency and duration of paracenteses before treatment initiation. In patients with minimal baseline ascites on imaging, its disappearance would meet the definition of MR. Moreover, in a patient with 2 baseline paracenteses, reduction to 1 paracentesis in a given period would fulfill criteria for a GPR. In these examples, it is unclear whether such nominal changes are clinically meaningful. Given the current lack of radiologic criteria for quantifying the volume of ascites, measuring the percent reduction might not be feasible. Accordingly, we propose the following criteria for ascites to be evaluable for response: (1) symptomatic presentation, and (2) requirement of medical intervention (eg, with diuretics) and/or paracenteses. For purposes of a clinical trial, paracentesis-dependent ascites requires the following criteria: (1) at least 2 episodes of therapeutic paracentesis in the 12 weeks before study enrollment, and (2) at least one of the procedures is performed within 6 weeks of drug start.

Similar to ascites, pleural effusion may develop in advanced SM, although it is an uncommon finding and has not been discussed in prior response criteria. We recommend that the evaluation and response criteria used for ascites be applied to pleural effusion (Table 3). Every attempt should be made to establish that the ascites or pleural effusion is related to SM and/or the associated myeloid neoplasm, including evaluation of MC content. Other causes of effusion should be excluded including infection, heart failure, and drugs such as dasatinib that have been used to treat advanced SM.

\subsection*{Hypoalbuminemia}

Hypoalbuminemia is an adverse prognostic factor for overall survival in SM\textsuperscript{38} and has been a component of the C finding “malabsorption with hypoalbuminemia and/or weight loss” in published response criteria.\textsuperscript{24} Hypoalbuminemia can reflect
Neither the baseline albumin level nor the absolute increase in albumin is considered an MR; however, this increase is of doubtful significance in order to be evaluable for response.

Nonhematologic

Liver function abnormalities

<table>
<thead>
<tr>
<th>Grade 2 abnormalities in direct bilirubin, AST, ALT, or AP†</th>
<th>Reversion of 1 or more liver function tests to normal range for ≥ 12 wk</th>
</tr>
</thead>
</table>

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 × 10⁹/L) | A minimum 100% increase in the ANC and an ANC of at least 0.5 × 10⁹/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 × 10⁹/L) | A minimum 100% increase in the platelet count and an absolute platelet count increase of at least 50 × 10⁹/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 × 10⁹/L | Transfusion-independence for a minimal period of 12 wk and maintenance of a platelet count of ≥ 20 × 10⁹/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.

†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.

Liver dysfunction

The challenge of defining response parameters related to hepatic function is severalfold. First, for patients with SM with associated myeloid neoplasm, it is unclear whether liver dysfunction is related to the SM or to the accompanying myeloid disease. Concomitant diseases such as MPN or MDS/MPN such as CMML, hypereosinophilic syndrome or chronic eosinophilic leukemia, or AML may (also) involve the liver (often via extramedullary hematopoiesis) and result in hepatitis-like disease or an obstructive hepatopathy. Liver biopsy is sometimes performed when the cause of hepatopathy is uncertain and may help to assess the grade and extent of liver involvement by SM. Although liver biopsy may be informative, the potential information gleaned from the procedure must be weighed against potential complications such as bleeding, especially in the setting of severe thrombocytopenia, coagulopathy, or ascites. In addition, similar to the unclear relationship between marrow MC burden and cytopenias, it is unknown what level of liver involvement by MCs consistently results in liver dysfunction.

Prior response criteria did not require a minimal baseline increase in liver function tests, and normalization of only a minimal increased level of total bilirubin, aspartate aminotransferase, or alanine aminotransferase would be sufficient to meet criteria for an MR. To maintain consistency with other findings of nonhematologic organ damage, we propose the requirement of a baseline Grade ≥ 2 increase (per Common Terminology Criteria of the direct bilirubin, aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase (AP) levels, to qualify for
response evaluation. Our experience is that the AP level is more frequently elevated in SM-related liver involvement compared with the other liver enzymes. In addition, the AP level seems to be a particularly useful marker and response parameter in patients with ASM and liver damage. The serum gamma-glutamyl transferase level is useful as a surrogate marker of the liver derivation of AP. For liver function abnormalities to be evaluable for response, they should be associated with ascites, clinically relevant portal hypertension, and/or liver MC infiltration that is (1) proven by biopsy, or (2) is likely to occur because of the presence of hepatomegaly or splenomegaly and the absence of other nonhematologic or hematologic causes that could contribute to abnormal liver function.

Organomegaly

Splenomegaly and hepatomegaly, without associated organ damage, have traditionally been referred to as B findings and are one defining feature of SSM (Table 2). Similarly, SM-related abdominal lymphadenopathy has been included in the category of B findings. Organomegaly by itself does not indicate inexorable progression to advanced SM or organ damage. However, even in the absence of organ damage, symptomatic splenomegaly may warrant therapeutic intervention similar to patients with myelofibrosis. We also advocate that palpable splenomegaly of more than 5 cm below the left costal margin with patient endorsement of spleen-related symptoms such as abdominal discomfort and/or early satiety be considered for response evaluation (CI) in clinical trials, even if organ damage per se is not present (Table 3). Whenever possible, we encourage 3D computed tomography or magnetic resonance imaging evaluation of changes in splenic volume to verify physical examination findings.

Hematologic organ damage

Cytopenias

The causes of cytopenias in advanced SM include compromise of normal marrow reserve by infiltration with neoplastic MCs, ineffective hematopoiesis in the context of SM with an associated myeloid neoplasm, hypersplenism, and other causes such as recent myelosuppressive therapy or gastrointestinal tract bleeding. The coexistence of a myeloid neoplasm often makes it difficult to ascertain the specific disease basis for low blood counts. This distinction is not relevant to ISM, where the relatively lower MC burden is not expected to contribute to cytopenias.

Anemia

Non-transfusion-dependent anemia. Prior response criteria required that for anemia to be evaluable, the baseline hemoglobin (Hb) level had to be less than 10 g/dL. MR was defined as an Hb level of more than 10 g/dL. A GPR was defined as a more than 50% reversion between the baseline Hb value and 10 g/dL, associated with a minimal increase of 1 g/dL. For the definition of MR, it is not specifically stated that the increase in Hb level must be at least 1 g/dL; therefore, an increase from 9.5 to 10.1 g/dL would constitute this higher level response, an improvement that may not be clinically relevant. We recommend that for non-transfusion-dependent anemia to be eligible for evaluation in clinical trials, the baseline range of anemia must be ≥ grade 2 (eg, Hb level < 10 g/dL) and must not be attributable to bleeding, hemolysis, or recent therapy.

We propose that in the setting of clinical trials, CI response for non-transfusion-dependent anemia requires an increase in Hb level of at least 2.0 g/dL that must be durable for at least 12 weeks, capped by a minimal Hb level of 8.5 g/dL. To meet criteria for the higher-quality response of a partial or complete remission (PR or CR), patients need to additionally achieve an absolute Hb level of at least 11 g/dL as well as meet all other defining criteria of a PR or CR (Table 4).

Transfusion-dependent anemia. Transfusion dependence is not addressed in prior response criteria, which can be problematic in clinical trials. Its definition and basis for response require more rigorous characterization. We recommend that a baseline RBC transfusion dependency be defined as (1) requiring a minimum of 6 units of RBC transfusions in the 12 weeks before the start of treatment, and (2) the most recent transfusion occurred in the previous 28 days before drug therapy. For clinical trials, patients should not be required to wait 12 weeks for study entry if 6 or more RBC transfusions are administered in a shorter window of time (the same applies to platelet transfusions; see below). In addition, RBC transfusions are only considered evaluable during the baseline and on-treatment periods if they are administered for a Hb level less than or equal to 8.5 g/dL and not considered related to bleeding, hemolysis, or treatment. In patients meeting criteria for baseline RBC transfusion dependence, a CI response is defined as transfusion independence for a minimal period of 12 weeks, while receiving protocol treatment, and with maintenance of a minimal Hb level of 8.5 g/dL at the end of the 12-week period. Partial reduction in transfusion requirements may translate into clinical benefit, but the usefulness of this endpoint is less clear than transfusion independence.

Thrombocytopenia

Non-transfusion-dependent thrombocytopenia. Thrombocytopenia at a platelet count of less than $10^5$/mL has been used as an evaluable cytopenia in prior response criteria. We propose that grade 2 thrombocytopenia ($<75\times10^9/L$) be used as the evaluable baseline platelet count for response evaluation in clinical trials. We define a CI response in the platelet count as a minimal 100% increase in the platelet count and an absolute platelet count increase of at least $50\times10^9/L$. In this current proposal, we make no distinction regarding whether thrombocytopenia is caused by BM involvement by MCs or hypersplenism.

Transfusion-dependent thrombocytopenia. Similar to transfusion-dependent anemia, no proposals exist in SM for defining and gauging response for transfusion-dependent thrombocytopenia. Although no specific platelet count is used as a threshold for transusing platelets, common clinical practice is to transfuse platelets for a platelet count of less than 10 to $20\times10^9/L$, or more than $10\times10^9/L$ in the presence of bleeding (eg, epistaxis, gum or gastrointestinal tract blood loss, or even in some cases of major bruising). For consistency with our aforementioned criteria for RBC transfusion dependency, we recommend that transfusion-dependent thrombocytopenia be defined as (1) the requirement of at least 6 units of apheresed platelets in the 12 weeks before the start of the study, with the most recent occurring in the prior 28 days; and (2) administration of transfusions only for a platelet count of less than $20\times10^9/L$. CI response in this category is defined as a platelet count of at least $20\times10^9/L$ maintained for at least 12 weeks after initiation of therapy and no platelet transfusions.

Neutropenia

In this current proposal, the absolute neutrophil count (ANC) may be evaluable for response if the baseline value is less than $1\times10^3/L$ (≥ grade 3). A CI response requires a minimal 100% increase in
by adding more specific criteria and histopathologic improvement. The intent is for these criteria to be incorporated as primary endpoints in clinical protocols so that novel agents can be compared in a reproducible manner. Given the poor prognosis of MCL, such patients should be treated without delay even in the uncommon circumstance in which organ damage (as outlined in Table 3) has not yet developed. In such cases, the primary endpoint should be based on reduction of the BM MC burden and serum tryptase level (eg, CR or PR).

Resolution of 1 or more findings of nonhematologic or hematologic organ damage without concomitant worsening of other eligible organ damage meets the definition of CI. (Table 4). Response categories of CR and PR are based on the percent reduction of (1) the burden of neoplastic MCs in the BM (and/or extracutaneous organ) and (2) the serum tryptase level (Table 4). In addition to changes in MC burden and serum tryptase level, achievement of a PR or CR requires that patients also meet criteria for resolution of at least 1 or all CI findings, respectively. The duration of CI response (as well as histopathologic markers of disease such as BM MC burden and serum tryptase level) must be at least 12 weeks.

the ANC and an ANC of at least $0.5 \times 10^9/L$ maintained for at least 12 weeks. Although prior criteria also required an ANC of less than $1 \times 10^9/L$ to be evaluable for response, only an increase in the ANC to at least $0.5 \times 10^9/L$ was required for response, which may have limited clinical importance and, in some cases, could be attributable to fluctuations in laboratory measurements.

Proposed IWG-MRT-ECNM response criteria for advanced SM

Our proposed new response criteria (Table 4) build on previously published systems and may be a valuable tool in clinical trials by adding more specificity to the evaluation of end-organ damage and histopathologic improvement. The intent is for these criteria to be incorporated as primary endpoints in clinical protocols so that novel agents can be compared in a reproducible manner. Given the poor prognosis of MCL, such patients should be treated without delay even in the uncommon circumstance in which organ damage (as outlined in Table 3) has not yet developed. In such cases, the primary endpoint should be based on reduction of the BM MC burden and serum tryptase level (eg, CR or PR).

Resolution of 1 or more findings of nonhematologic or hematologic organ damage without concomitant worsening of other eligible organ damage meets the definition of CI. (Table 4). Response categories of CR and PR are based on the percent reduction of (1) the burden of neoplastic MCs in the BM (and/or extracutaneous organ) and (2) the serum tryptase level (Table 4). In addition to changes in MC burden and serum tryptase level, achievement of a PR or CR requires that patients also meet criteria for resolution of at least 1 or all CI findings, respectively. The duration of CI response (as well as histopathologic markers of disease such as BM MC burden and serum tryptase level) must be at least 12 weeks.

Table 4. IWG-MRT-ECNM consensus response criteria for patients with ASM, MCL, and SM associated with a myeloid neoplasm

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete remission (CR)*</td>
<td>Requires all 4 criteria and response duration must be ≥ 12 wk</td>
</tr>
<tr>
<td>No presence of compact neoplastic mast cell aggregates in the BM or other biopsied extracutaneous organ</td>
<td></td>
</tr>
<tr>
<td>Serum tryptase level &lt; 20 ng/mL†</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood count remission defined as ANC ≥ $1 \times 10^9/L$ with normal differential, Hb level ≥ 11 g/dL, and platelet count ≥ $100 \times 10^9/L$</td>
<td></td>
</tr>
<tr>
<td>Complete resolution of palpable hepatosplenomegaly and all biopsy-proven or suspected SM-related organ damage (CI findings)‡</td>
<td></td>
</tr>
<tr>
<td>Partial remission (PR)*</td>
<td>Requires all 3 criteria and response duration must be ≥ 12 wk, in the absence of both CR and progressive disease (PD)</td>
</tr>
<tr>
<td>Reduction by ≥ 50% in neoplastic MCs in the marrow and/or other extracutaneous organ at biopsy demonstrating eligible SM-related organ damage</td>
<td></td>
</tr>
<tr>
<td>Reduction of serum tryptase level by ≥ 50%†</td>
<td></td>
</tr>
<tr>
<td>Resolution of 1 or more biopsy-proven or suspected SM-related organ damage (CI finding(s))‡</td>
<td></td>
</tr>
<tr>
<td>Clinical improvement (CI)*</td>
<td>Response duration must be ≥ 12 wk</td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>Not meeting criteria for CR, PR, CI, or PD</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>Requires at least 1 element of either criteria 1 or 2 and duration must be ≥ 8 wk</td>
</tr>
<tr>
<td>(1) For patients with baseline grade 2 nonhematologic organ damage: a) worsening by 1 grade, AND b) minimum 100% increase (doubling) of laboratory abnormality.</td>
<td></td>
</tr>
<tr>
<td>For patients with baseline grade 2 albumin: (a) worsening by 1 grade, AND (b) decrease by ≥ 0.5 g/dL.</td>
<td></td>
</tr>
<tr>
<td>For patients with baseline grade 3 nonhematologic organ damage: minimum 100% increase (doubling) of laboratory abnormality.</td>
<td></td>
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<tr>
<td>For patients with baseline grade 2 transfusion-independent anemia or thrombocytopenia: New transfusion dependence of ≥ 4 units of RBCs or platelets at 8 wk.</td>
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<tr>
<td>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</td>
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<tr>
<td>For patients with baseline grade ≥ 3 neutropenia: (a) &gt; 50% decrease in neutrophil count, AND (b) absolute decrease of neutrophil count of ≥ 250/mm³, AND c) grade 4</td>
<td></td>
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<tr>
<td>(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 &gt; 5 cm, a &gt; 50% worsening and development of at least 10 cm of palpable symptomatic splenomegaly compared with the baseline value.¶</td>
<td></td>
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<tr>
<td>Loss of response (LOR)</td>
<td>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.</td>
</tr>
</tbody>
</table>

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 findings. (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%.
The criteria for stable disease, PD, and loss of response are also detailed in Table 4. In contrast to the 12-week minimum required for a response, an 8-week duration is required for PD and loss of response. This 8-week time window balances the need to verify clinically meaningful disease progression while not having patients continue to receive ineffective therapy for an inappropriately long duration to be assigned the status of PD or loss of response. In some patients with advanced SM with accelerating signs of disease, the ability to achieve stable disease may be considered a success in light of current treatment options.

**Secondary endpoints in trials of advanced SM**

In these proposed IWG-MRT-ECNM response criteria, several organ findings are purposefully not included as evaluable primary endpoints. The 2 reasons are that (1) the clinical relevance is low concerning the need to treat (eg, < grade 2 nonhematologic organ damage or subthreshold cytopenias/transfusion dependence), and (2) the organ damage is difficult to quantify (eg, weight loss and bone lesions). Such cases of noneligible organ damage should be descriptively reported as secondary endpoints in clinical trials, by way of median values, percent change, and confidence intervals to ascertain clinical and statistical significance. Some trials may choose to incorporate a composite of several secondary individual endpoints as the basis for a study’s primary objective, or as one of its secondary objectives. This may allow a broader picture of the quality and duration of a drug’s activity. The supplemental Appendix discusses the rationale for considering certain nonhematologic and hematologic organ damage as secondary endpoints as well as additional disease features including KIT mutation status, cytogenetic abnormalities, mediator symptoms/quality of life, and cutaneous involvement. Supplemental Table 3 proposes specific eligibility and response criteria for these secondary endpoints in the context of clinical trials, although protocols may adopt modifications of these recommendations.

**Evaluation of the associated myeloid neoplasm**

Although it has been reported that approximately 30% of cases with SM are associated with a myeloid neoplasm, the frequency may be variable and likely reflects referral bias. The ability to identify a concomitant SM or myeloid neoplasm may depend on several factors, including the expertise of the evaluating pathologist, and whether 1 disease is masked by the presence of another. For example, unmasking of MC aggregates typically occurs after induction chemotherapy and achievement of BM hypoplasia of

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Table 5. Shared and unique clinicopathologic features between SM and various myeloid neoplasms: potential endpoints for assessment of response in the myeloid neoplasm

<table>
<thead>
<tr>
<th>Myeloid neoplasm</th>
<th>Shared features with advanced SM</th>
<th>Distinguishing features from pure SM</th>
<th>Unique myeloid neoplasm endpoints to measure</th>
<th>Published response criteria for the myeloid neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>Cytopenias</td>
<td>Dysplasia, increased myeloblasts, ring sideroblasts</td>
<td>Reduction in dysplasia, myeloblasts, % ring sideroblasts</td>
<td>Modified IWG criteria [56]</td>
</tr>
<tr>
<td>CMML</td>
<td>Cytopenias, organomegaly/LAN</td>
<td>Dysplasia, monocytosis, increased myeloblasts, ring sideroblasts</td>
<td>Reduction in dysplasia, monocytosis, myeloblasts, % ring sideroblasts</td>
<td>Modified IWG criteria [56]</td>
</tr>
<tr>
<td>MDS/MPN (excluding CMML)</td>
<td>Cytopenias, organomegaly/LAN</td>
<td>Dysplasia, leukocytosis</td>
<td>Reduction in dysplasia, myeloblasts, % ring sideroblasts</td>
<td>None</td>
</tr>
<tr>
<td>HES or CEL-NOS, or myeloid neoplasms with eosinophilia and rearrangement of PDGFRA/B or FGFR1</td>
<td>Eosinophilia, organomegaly/LAN, elevated tryptase level</td>
<td>± Leukocytosis</td>
<td>Reduction in leukocytosis &amp; eosinophilia; FISH or PCR for PDGFRA/B, FGFR1-rearranged</td>
<td>None; a proposed definition includes: complete hematologic response (CR); normalization of eosinophilia, and if present, leukocytosis; partial hematologic response (PR); ≥ 50% improvement of absolute eosinophilia</td>
</tr>
<tr>
<td>Myelofibrosis (primary or secondary)</td>
<td>Cytopenias, organomegaly, marrow fibrosis</td>
<td>Leukocyte-blastosis, increased myeloblasts, JAK2 V617F mutation, % increased LDH level</td>
<td>Reduction in leukocyte-blastosis, myeloid immaturity, and % peripheral blood and BM myeloblasts; reduction of JAK2 V617F allele burden by quantitative RT-PCR</td>
<td>IWG-MRT response criteria [57]</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Cytopenias, organomegaly</td>
<td>Increased myeloblasts; recurrent cytogenetic abnormalities (eg, t(8,21); t(15;17); inv(16) or t(16;16); AML-associated mutations such as FLT3, NPM1, and CEBP-a)</td>
<td>Reduction in myeloblasts; remission of AML-related cytogenetic abnormalities</td>
<td>IWG response criteria [58]</td>
</tr>
</tbody>
</table>

*The presence of a PDGFRA/B or FGFR1-rearranged myeloid neoplasm with eosinophilia with KIT D816V-positive SM is extremely rare.

CEL-NOS, chronic eosinophilic leukemia not otherwise specified; FISH, fluorescent in situ hybridization; HES, hypereosinophilic syndrome; LAN, lymphadenopathy; LDH, lactate dehydrogenase; RT-PCR, reverse transcription polymerase chain reaction.
what was initially considered “pure” AML. Conventional wisdom has been that prognosis in SM with an associated myeloid neoplasm usually relates to the myeloid disease component. However, outcomes may vary according to the specific type of myeloid neoplasm, highlighting the need to distinguish MDS vs MPN vs MDS/MPN vs AML. The clinical approach for such patients has been to treat the SM component as if the myeloid neoplasm were not present and to treat the myeloid neoplasm as if the SM were not present. Because KIT D816V or other pathogenetic abnormalities may reside in both the neoplastic MCs and associated myeloid clonal cell populations, published for some of these myeloid diseases, and they may pathologic features that are common to and unique between SM brosis, dysplasia, hypersplenism, and myelosuppression from prior Cytopenia(s) can be confounded by other factors such as BM population; however, this distinction may not always be feasible. times be inferred by the degree of BM involvement by each disease the accompanying myeloid neoplasm to cytopenia(s) may some- the case of BM involvement, the relative contribution(s) of SM or may vary according to the specific type of myeloid neoplasm, rest with the discretion of the individual investigator and patient. In forthcoming trials, the usefulness and validity of the current response criteria should be compared with adjudication schemes that have been published.

Distinguishing nonhematologic or hematologic organ damage due to the SM component vs the associated myeloid disease can be very difficult, if not impossible, in some patients. Some have ad- vocated biopsy of the involved extramedullary organ to elucidate the burden of neoplastic MCs vs associated myeloid neoplasm. In the case of BM involvement, the relative contribution(s) of SM or the accompanying myeloid neoplasm to cytopenia(s) may sometimes be inferred by the degree of BM involvement by each disease population; however, this distinction may not always be feasible. Cytopenia(s) can be confounded by other factors such as BM fi- brosis, dysplasia, hypersplenism, and myelosuppression from prior therapy. Table 5 provides guidance for evaluating the clinicopathologic features that are common to and unique between SM and various myeloid neoplasms. Response criteria have been published for some of these myeloid diseases, and they may be used in addition to these SM criteria to generate a more complete assessment of benefit. We recommend that responses related to the myeloid neoplasm be reported as secondary endpoints in clinical trials. For some trials enrolling patients with SM and an associated myeloid neoplasm, eligibility may require that organ damage be either proven or suspected to be related to MC infiltration. However, other trials may not require that organ damage be attributed to a specific disease component; instead, they may only require that it is present.

Concluding remarks

The response criteria outlined herein are intended to provide a common framework for adjudicating responses as part of the rigorous clinical trial evaluation of novel agents for patients with advanced SM and organ damage. The thresholds used to define organ damage and CI are intended to be more specific and quantifiable than prior criteria and should allow more direct and clinically useful comparisons across trials. Because of these stricter thresholds for eligible hematologic and nonhematologic organ damage, fewer patients may be candidates for the primary trial endpoints we have outlined. However, some patients with mild organ damage may not require immediate treatment with cyto-reductive therapy. Ultimately, the decision to initiate treatment rests with the discretion of the individual investigator and patient. In forthcoming trials, the usefulness and validity of the current response criteria should be compared with adjudication schemes that have been published.

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Authorship

Contribution: J.G., P.V., A.T., A.P., and S.V. had primary responsibility for formulating the response criteria. J.G., P.V., and A.T. had primary responsibility for writing the manuscript; all authors contributed to the review and revision of the response criteria and the manuscript.

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Correspondence: Jason Gotlib, MD, MS, Associate Professor of Medicine (Hematology), Stanford Cancer Institute, 875 Blake Wilbur Drive, Room 2324, Stanford, CA 94305-5821; e-mail: jason. gotlib@stanford.edu.

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International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis

Jason Gotlib, Animesh Pardanani, Cem Akin, Andreas Reiter, Tracy George, Olivier Hermine, Hanneke Kluin-Nelemans, Karin Hartmann, Wolfgang R. Sperr, Knut Brockow, Lawrence B. Schwartz, Alberto Orfao, Daniel J. DeAngelo, Michel Arock, Karl Sotlar, Hans-Peter Horny, Dean D. Metcalfe, Luis Escribano, Srdan Verstovsek, Ayalew Tefferi and Peter Valent