Proposed European Competence Network on Mastocytosis

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Proposed European Competence Network on Mastocytosis—American Initiative in Mast Cell Diseases (ECNM-AIM) Response Criteria in Advanced Systemic Mastocytosis

Jason Gotlib, MD, MS[a], Juliana Schwaab, MD[b], William Shomali, MD[a], Tracy I. George, MD[c], Deepti H. Radia, MD[d], Mariana Castells, MD, PhD[e], Melody C. Carter, MD[f], Karin Hartmann, MD[g,h], Ivan Álvarez-Twose, MD, PhD[i], Knut Brockow, MD[j], Patrizia Bonadonna, MD[k], Olivier Hermine, MD, PhD[l], Marek Niedoszytko, MD, PhD[m], Gregor Hoermann, MD, PhD[n,o], Wolfgang R. Sperr, MD[o,p], Hanneke Oude Elberink, MD[q], Frank Siebenhaar, MD[r,s], Joseph H. Butterfield, MD[t], Celalettin Ustun, MD[u], Roberta Zanotti, MD[v], Massimo Triggiani, MD, PhD[w], Lawrence B. Schwartz, MD, PhD[x], Jonathan J. Lyons, MD, PhD[y], Alberto Orfao, MD, PhD[z], Karl Sotlar, MD[aa], Hans-Peter Horny, MD[bb], Michel Arock, MD, PhD[cc], Dean D. Metcalfe, MD, MS[f], Cem Akin, MD, PhD[dd], Johannes Lübke, MD[b], Peter Valent, MD[o,p], and Andreas Reiter, MD[b] *Mannheim, Munich, and Berlin, Germany; London, United Kingdom; Basel, Switzerland; Toledo and Salamanca, Spain; Verona and Salerno, Italy; Paris, France; Gdansk, Poland; Vienna and Salzburg, Austria; and Groningen, The Netherlands; and Stanford, Calif; Salt Lake City, Utah; Boston, Mass; Bethesda, Md; Rochester, Minn; Chicago, Ill; Richmond, Va; and Ann Arbor, Mich*

Advanced systemic mastocytosis (AdvSM) is characterized by the presence of *KIT* D816V and other somatic mutations (eg, in *SRSF2*, *ASXL1*, and *RUNX1*) in 95% and 60% to 70% of patients, respectively. The biological and clinical consequences of AdvSM include multilineage involvement (eg, associated hematologic neoplasm) in 60% to 80% of patients, variable infiltration and damage (C-findings) of predominantly bone marrow and visceral organs through affected mast cell (MC) and non-MC lineages, and elevated levels of serum tryptase. Recently, the treatment landscape has substantially changed with the introduction of the multikinase/*KIT* inhibitor midostaurin and the selective *KIT* D816V inhibitor avapritinib. In this review, we discuss the evolution of AdvSM response criteria that have been developed to better capture clinical benefit (eg, improved responses and progression-free and overall survival). We propose refined response criteria from European Competence Network on Mastocytosis and American Initiative in Mast Cell Diseases investigators that use a tiered approach to segregate the effects of histopathologic (eg, bone marrow MC burden, tryptase), molecular (eg, *KIT* D816V variant allele frequency), clinical (eg, C-findings), and symptom response on long-term outcomes. These response criteria require evaluation in future prospective clinical trials of selective *KIT* inhibitors and other novel agents. **(J Allergy Clin Immunol Pract 2022;10:2025-38)**

Key words: *Advanced systemic mastocytosis; International Working-Group for Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; Midostaurin; Avapritinib; Pure pathologic response; KIT D816V*

[a]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, Calif
[b]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany
[c]Department of Pathology, University of Utah, Salt Lake City, Utah
[d]Department of Clinical Haematology, Guys and St Thomas' NHS Hospitals, London, United Kingdom
[e]Division of Allergy and Immunology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass
[f]Mast Cell Biology Section, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md
[g]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland
[h]Department of Biomedicine, University Hospital Basel and University of Basel, Switzerland
[i]Instituto de Estudios de Mastocitosis de Castilla La Mancha and Centro de Investigación Biomédica en Red de Oncología (CIBERONC), Hospital Virgen del Valle, Toledo, Spain
[j]Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany
[k]Allergy Unit, Verona University Hospital, Verona, Italy
[l]Imagine Institute Université de Paris, Sorbonne, INSERM U1163, Centre National de Référence des Mastocytoses, Hôpital Necker, Assistance Publique Hôpitaux de Paris, Paris, France
[m]Department of Allergology, Medical University of Gdansk, Gdansk, Poland
[n]MLL Munich Leukemia Laboratory, Munich, Germany
[o]Ludwig Boltzmann Institute for Hematology and Oncology, Medical University of Vienna, Vienna, Austria
[p]Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria
[q]Department of Allergology, University Medical Center Groningen and GRIAC Research Institute, University of Groningen, Groningen, The Netherlands
[r]Institute of Allergology, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
[s]Department of Allergology and Immunology, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany
[t]Division of Allergic Diseases, Mayo Clinic, Rochester, Minn
[u]Department of Medicine, Division of Hematology, Oncology, and Cell Therapy, Coleman Foundation Blood and Marrow Transplant Center at Rush University Medical Center, Chicago, Ill
[v]Section of Hematology, Multidisciplinary Outpatients Clinics for Mastocytosis, Department of Medicine, University Hospital of Verona, Verona, Italy

Abbreviations used

AdvSM- *Advanced systemic mastocytosis*
AdvSM-SAF- *AdvSM symptom assessment form*
AHN- *Associated hematologic neoplasm*
AIM- *American Initiative in Mast Cell Diseases*
AML- *Acute myeloid leukemia*
AP- *Alkaline phosphatase*
ASM- *Aggressive systemic mastocytosis*
BM- *Bone marrow*
CI- *Clinical improvement*
CR- *Complete remission*
CRh- *CR with partial hematologic recovery*
ddPCR- *Digital droplet polymerase chain reaction*
EAB- *Expressed allele burden*
ECNM- *European Competence Network on Mastocytosis*
EMA- *European Medicines Agency*
EORTC- *European Organization for Research and Treatment of Cancer*
FDA- *US Food and Drug Administration*
GPSM- *Global Prognostic Score for Mastocytosis*
IPSM- *International Prognostic Scoring System for Mastocytosis*
ISM- *Indolent systemic mastocytosis*
IWG-MRT-ECNM- *International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis*
LOD- *Limit of detection*
MARS- *Mutation-adjusted risk score*
MC- *Mast cell*
MCL- *Mast cell leukemia*
MDS- *Myelodysplastic syndrome*
NGS- *Next-generation sequencing*
OS- *Overall survival*
PB- *Peripheral blood*
PCR- *Polymerase chain reaction*
PD- *Progressive disease*
PFS- *Progression-free survival*
PPR- *Pure pathologic response*
PR- *Partial remission*
PRO- *Patient-reported outcome*
QLQ-C30- *Quality of life questionnaire core model*
QoL- *Quality of life*
SD- *Stable disease*
SM- *Systemic mastocytosis*
SM-AHN- *Systemic mastocytosis with an associated hematologic neoplasm*
SSM- *Smoldering systemic mastocytosis*
VAF- *Variant allele frequency*
WHO- *World Health Organization*

INTRODUCTION

Systemic mastocytosis (SM) is driven by the *KIT* D816V mutation in 95% of adult patients.[1-3] Its presence in MC and variably in non-MC, which reflects multilineage involvement,[4] accounts for several morphologically and clinically well-defined subtypes, including bone marrow (BM) mastocytosis, indolent SM (ISM), smoldering SM (SSM), and advanced SM (AdvSM).[5] Advanced SM is an umbrella term composed of aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL). One or more C-findings (SM-related organ damage) are needed for the diagnosis of ASM, the presence of both SM and an AHN is necessary for the diagnosis of SM-AHN, and infiltration by 20% or more MCs on a BM aspirate smear is required for the diagnosis of MCL.[5,6] Although most patients with SM-AHN or MCL have one or more C-findings, the presence of such findings is not required for the diagnosis of these two subtypes of AdvSM.[6]

In the transition from ISM to SSM and AdvSM, a common underlying feature that emerges is an increased propensity for multilineage involvement of *KIT* D816V[4] and a multimutated state characterized by somatic mutations beyond *KIT* D816V.[7] Thus, the genetic profile of AdvSM is complex and is characterized by the presence of additional somatic mutations in 60% to 70% of patients, which are strikingly similar to those identified in other myeloid neoplasms (eg, *SRSF2, ASXL1, RUNX1, TET2, DNMT3A, JAK2, CBL, NRAS*).[8] The overall genetic profile and the variant allele frequency (VAF) in individual genes substantially affect clinical phenotype, (potential) response to treatment, and prognosis, in which mutations in one or more of the *SRSF2*, *ASXL1*, and/or *RUNX1* (eg, *S/A/R* gene panel) genes are associated with a poorer prognosis.[9,10] The clinical consequences of proliferation and accumulation of neoplastic MC in various organ systems, predominantly BM, skin, and gastrointestinal organs, are categorized through B-findings (high disease burden often associated with organ enlargement, such as hepatosplenomegaly) and C-findings.[5,11]

KIT inhibition is now validated as a clinical treatment strategy in AdvSM.[12] Nonrandomized, registrational trials supporting the multikinase/*KIT* inhibitor midostaurin[13,14] and the *KIT* D816 selective inhibitor avapritinib[15,16] led to their approvals by regulatory agencies in 2017 (midostaurin by the US Food and Drug Administration [FDA] and European Medicines Agency [EMA]) and 2021/2022 (avapritinib by the FDA [first-line therapy] and EMA [second-line therapy]). These trials, which included central adjudication of clinicopathologic responses, have provided additional lessons about the relative strengths, weaknesses, and

[w]Division of Allergy and Clinical Immunology, University of Salerno, Salerno, Italy
[x]Department of Internal Medicine, Division of Rheumatology, Allergy, and Immunology, Virginia Commonwealth University, Richmond, Va
[y]Translational Allergic Immunopathology Unit, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md
[z]Servicio Central de Citometria (NUCLEUS), Instituto de Biología Molecular y Celular del Cáncer (IBMCC) Instituto Biosanitario de Salamanca, CIBERONC and Department of Medicine, University of Salamanca, Salamanca, Spain; Utah
[aa]Institute of Pathology, Paracelsus Medical University Salzburg, Salzburg, Austria
[bb]Institute of Pathology, Ludwig-Maximilians-University, Munich, Germany
[cc]Department of Hematological Biology, Pitié-Salpêtrière Hospital, Pierre et Marie Curie University, Paris, France
[dd]Division of Allergy and Clinical Immunology, University of Michigan, Ann Arbor, Mich

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opportunities for improvement in the response criteria used to assess novel therapies in AdvSM.

ESSENTIAL CHARACTERISTICS FOR RESPONSE ASSESSMENT

Bone marrow

Qualitative and quantitative assessments of BM morphology include characterization of dense clusters of MC using the immunohistochemical markers tryptase, CD117, and CD25 (and sometimes CD2 and CD30) to assess the MC burden.[5-7,17,18] During *KIT* inhibitor therapy, reduction or elimination of MC aggregates was observed over 3 to 12 months.[7,13-16,19] Other BM findings include normalization of BM cellularity, loss of expression of CD25 on MC, reversion of MC morphology from a spindled to a round shape, and reduction in peri-MC aggregate fibrosis. In some cases, a scattered, interstitial pattern of MC may be found as dense clusters of MC resolve.[7,20] During therapy, serial changes in MC burden are best confirmed in two consecutive trephine core biopsies during the first 3 to 12 months.

Peripheral blood

Causes of cytopenias in AdvSM are multifactorial. These include impaired BM hematopoiesis owing to MC infiltration and/or an AHN with or without BM dysplasia and/or fibrosis or sclerosis, inflammation, toxicity of treatment, and hypersplenism. Anemia may relate to various causes including chronic disease, hypersplenism, and from iron deficiency caused by malabsorption from MC infiltration of the small intestines and more rarely from acute or chronic gastrointestinal bleeding (eg, owing to esophageal varices). Cytopenias are the most relevant C-findings for prognostication (eg, mutation-adjusted risk score, Mayo Alliance Prognostic System for Mastocytosis, International Prognostic Scoring System for Mastocytosis [IPSM], Global Prognostic Score for Mastocytosis), and response assessment.[20-23]

Careful attention should be paid to signs of multilineage involvement in the peripheral blood (PB) (eg, leukocytosis, erythrocytosis, thrombocytosis, monocytosis, eosinophilia, dysplasia, blasts) and BM (eg, hypercellularity, dysplasia in various lineages, monocytosis, eosinophilia, diffuse fibrosis, sclerosis, increased blasts) as basis for the diagnosis of an AHN, which in most patients is of a myeloid phenotype.[5,6,24] The most frequent subtypes of AHN include chronic myelomonocytic leukemia (CMML), myelodysplastic/myeloproliferative syndrome-unclassifiable (MDS/MPN-u), MDS, chronic eosinophilic leukemia (CEL), and acute myeloid leukemia (AML). Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) is typically associated with the presence of additional somatic mutations.[8] Importantly, the *KIT* D816V mutation can be found in cells derived from the myeloid AHN.[4,25,26] Both midostaurin and avapritinib have decreased or normalized PB monocytosis and eosinophilia in patients with SM-CMML and SM-CEL.[13-16] Leukocytosis and thrombocytosis are usually found only in the presence of an associated chronic myeloid neoplasm. In such cases, additional somatic mutations (eg, *JAK2*, *SRSF2*, or *SF3B1)* are often identified on next-generation sequencing (NGS). An initial diagnosis of SM with AML may be encountered,[27,28] but it may also occur over time as a result of transformation of a chronic myeloid AHN.

Clinical chemistries

The most important serum marker for diagnosis, prognostication (IPSM) and response monitoring of AdvSM is the serum tryptase level.[5-7,29] However, individual levels need careful interpretation and may exhibit fluctuation, which should not be overinterpreted as a meaningful change. A normal serum tryptase (or a level less than the minor diagnostic criterion threshold of 20 ng/mL) does not exclude the diagnosis of SM. Although the absolute level of tryptase may correlate with MC burden, it may not necessarily correlate with C-findings or with the overall disease burden, which in SM-AHN is composed of *KIT*

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has been a consultant for Third Harmonic Bio; and has been on the data safety monitoring board of AB Science. M.C. Carter has been an investigator in a clinical trial for Sanofi US Services. K. Hartmann has received research funding from Euroimmun and Thermo Fisher; and has been a consultant and received honoraria from Allergopharma, ALK-Abello, Blueprint Medicines, Deciphera, Leo Pharma, Menarini, Novartis, Pfizer, Takeda, and Thermo Fisher. I. Álvarez-Twose has been a consultant and received honoraria from Novartis and Blueprint Medicines. K. Brockow has been on the advisory board and received honoraria from Blueprint Medicines. O. Hermine is the cofounder and a stock holder of AB Science; and has received research grants from AB Science, Novartis, Celgene, and Lipomed. M. Niedoszytko has received honoraria from ALK and Novartis and support in clinical trials from AB Science and Novartis. G. Hoermann has been a consultant and received honoraria from Novartis and Incyte. W.R. Sperr has been a consultant and received honoraria from Thermo Fisher, AbbVie, Novartis, Pfizer, Incyte, Deciphera, Jazz, Teva, and BMS-Celgene. F. Siebenhaar has been a speaker and/or advisor for and/or has received research funding from Allakos, Blueprint, Celldex, Cogent Biosciences, Genentech, Novartis, Moxie, Sanofi, and Uriach. C. Ustun has been on the advisory board for and received honoraria from Blueprint Medicines. R. Zanotti has been a consultant for and received honoraria from Novartis, Deciphera, and Blueprint Medicines. M. Triggiani has been a consultant for and received honoraria from Novartis, Deciphera, and Blueprint Medicines; and has been an investigator in a clinical trial for Blueprint Medicines. L.B. Schwartz receives royalties through Virginia Commonwealth University for the tryptase assay that are shared with LBS (Thermo Fisher); received grants through LBS as site primary investigator from Novartis for their midostaurin and from Deciphera for their ripretinib in advanced mastocytosis clinical trials; and has been on the advisory board for Deciphera and Blueprint Medicines. A. Orfao has been a consultant for and received honoraria from Novartis and Blueprint Medicines. K. Sotlar has been on the advisory board of and received honoraria from Novartis. H.-P. Horny has been on the advisory board for and received honoraria from Novartis, Deciphera, and Blueprint Medicines. M. Arock has received research grants from Blueprint and Deciphera; and honoraria from Blueprint Medicines and Deciphera. C. Akin has been a consultant for and received honoraria from Blueprint Medicines and Novartis; has received a research grant from Blueprint Medicines; and was an investigator in a clinical trial for Blueprint Medicines. D.D. Metcalfe was an investigator in a clinical trial for Sanofi US Services. P. Valent has been on the advisory board for and received honoraria from Novartis, Blueprint Medicines, Deciphera, Celgene, and Incyte. A. Reiter received research grant (funds for administration of clinical trials) from Blueprint Medicines, Novartis, and Deciphera; has been on the advisory board of and received honoraria from Blueprint Medicines and Novartis; and was reimbursed for travel expenses by Blueprint Medicines and Novartis. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Jason Gotlib, MD, MS, Division of Hematology, Stanford Cancer Institute/Stanford University School of Medicine, 875 Blake Wilbur Dr, Rm 2324, Stanford, Calif 94305-6555. E-mail: jason.gotlib@stanford.edu.

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D816V-positive MC and frequently other myeloid non-MC lineages.[7,25,26]

Another important serum marker is alkaline phosphatase (AP), which is often elevated in AdvSM.[10] Elevation of AP, not direct bilirubin, AST, or ALT, is the most common presentation of liver involvement by MC disease. The causes of hypoalbuminemia are also multifactorial, most importantly through liver dysfunction but also through inflammation and/or malabsorption. Alkaline phosphatase and albumin are easily accessible and inexpensive response parameters. An initial AP elevation may be observed in patients responding to *KIT* inhibitors.[13-16] Other frequently elevated serum markers include total protein, ß2-microglobulin, and vitamin B12. Whereas the lactate dehydrogenase is usually low or normal in ASM and MCL, an elevated lactate dehydrogenase is strongly associated with a SM-AHN.[30]

Other organ dysfunction

Organomegaly, specifically hepatosplenomegaly, can be seen in most patients with AdvSM. However, associated organ dysfunction distinguishes AdvSM from SSM. Hepatic dysfunction can present with a complex and variable pattern ranging from mild elevation of liver function tests to severe dysfunction including hypoalbuminemia and portal hypertension (eg, esophageal varices, splenomegaly, and ascites). A marked reduction of hepatomegaly, but more importantly splenomegaly, has been observed in patients who respond to midostaurin or avapritinib. Conversely, when these organs increase in size during therapy, this can serve as a clinical indicator of disease resistance or progression. Pleural effusions are most frequently caused by hypoalbuminemia and/or portal hypertension. Bowel infiltration is associated with diarrhea and malabsorption, and sometimes marked weight loss. For unknown reasons, clinically significant MC infiltration of the lungs, heart, and kidneys resulting in organ dysfunction seems to be rare. However, subclinical infiltration may go undetected because histopathologic examination of these organs is less frequently performed. Osteoporosis is a characteristic feature of ISM, but it is less common in AdvSM.[31,32] Typical features of AdvSM include increased bone mineral density and osteosclerosis; in fact, the radiographic appearance of what appear to be osteolytic lesions may actually represent normal BM surrounded by osteosclerosis in some cases. Very rare, large (>2 cm) osteolytic lesions qualify for a diagnosis of AdvSM; when feasible, a bone biopsy is recommended to confirm involvement by neoplastic MC.[11] Bone fractures are considered C-findings only when they are the consequence of osteolytic lesions, not when they are a result of osteoporosis.

Molecular genetics

The *KIT* D816V mutation is an obvious target for assessing a molecular response. Quantitative allele-specific polymerase chain reaction (PCR) or digital droplet PCR (ddPCR) assays at the DNA (VAF) or RNA/cDNA (expressed allele burden [EAB]) level with a sensitivity down to 0.01% to 0.1% are gaining widespread use.[1,2,33-35] Next-generation sequencing panels, which exhibit a lower sensitivity, typically in the range of 1% to 5%, may produce false negatives and are not considered adequate for screening for *KIT* D816V or for serial monitoring of molecular response, particularly when *KIT* D816V VAF is less than 1%.[2,3,7,11,36]

In patients with AdvSM who are receiving treatment with *KIT* inhibitors, a marked reduction of the *KIT* D816V EAB on midostaurin or even PCR negativity at the DNA level on avapritinib has been demonstrated. In 28 *KIT* D816V-positive patients with at least 6 months on midostaurin, quantitative real-time reverse-transcriptase PCR was performed before the first dose of treatment and every 3 months while receiving treatment.[37] A significant reduction in the *KIT* D816V EAB of 25% or greater at month 6 was the strongest on-treatment predictor for improved survival in a multivariable analysis and was superior to many single parameters, including the Valent response criteria. In contrast, seven of eight *KIT* nonresponders had an increase in *KIT* D816V EAB during follow-up.[37] These data on the impact of *KIT* D816V EAB reduction of 25% or greater at 6 months on overall survival (OS) were corroborated in a registry study of 62 midostaurin-treated patients.[38]

In the phase I EXPLORER trial of avapritinib, in which ddPCR with a limit of detection (LOD) of 0.17% was used, the *KIT* D816V VAF in BM was reduced from baseline by 50% or more in 80% of patients and became undetectable in 30% of patients.[15] However, it must be further evaluated whether PCR negativity originating from a VAF of less than 10% to 20% is as relevant as that coming from greater than 30% to 50%. In addition, the depth of clinical response generally correlated with the elimination of measurable *KIT* D816V. In a *post hoc* analysis of EXPLORER using best-modified IWG (mIWG) response criteria, complete elimination of measurable *KIT* D816V occurred in 63% of patients with a complete response (CR) (n = 8), in 50% of patients with a CR with partial hematologic recovery (CRh) (n = 8), in 23% of patients with a partial response (PR) (n = 13), and in only 15% of patients with clinical improvement (CI) (n = 2) or stable disease (SD) (n = 11).[15]

Because almost all patients with *KIT* D816V-positive AdvSM have a measurable allele burden in PB at diagnosis, regular measurements of the *KIT* D816V VAF/EAB should be performed at the routine follow-up during treatment with *KIT* inhibitors, chemotherapy, and/or allogeneic hematopoietic stem cell transplantation. A recent analysis using highly sensitive, next-generation flow cytometry showed that circulating tumor MCs were highest in AdvSM compared with non-advanced SM patients.[39] In addition, a statistically significant, nonlinear correlation was found between PB circulating tumor MC counts and *KIT* D816V VAF in both PB and BM.[39] Although this suggests a general concordance between the MC tumor burden in the PB and BM, we recommend that complete molecular remission in the PB be confirmed in the BM. Molecular responses, including the relative reduction of VAF/EAB at 3 or 6 months, and the timing and duration of PCR negativity (if achieved), require further assessment regarding their impact on long-term disease outcomes, and how best to incorporate them in clinical decision-making.

Impact of additional somatic mutations and cytogenetic abnormalities

Further data have highlighted the potential progression of *KIT* D816V-independent subclones, possibly even while the patient is otherwise in major or complete remission of the SM component.[37] A significant increase in the VAF of preexisting additional somatic mutations (eg, *IDH2*, *KRAS*) was observed in two patients and the emergence of new somatic mutations (eg, *NPM1*, *RUNX1*) was found in association with progression to secondary

AML in two other patients. Serial NGS analysis of seven deceased patients revealed the acquisition of new somatic mutations (eg, *RUNX1*, *K/NRAS*, *IDH*, or *NPM1*) and/or increasing VAF of preexisting somatic mutations, while *KIT* D816V EAB was increasing (n = 4) or remained stable or low (n = 3).[37]

An aberrant karyotype is identified in up to 20% to 30% of SM-AHN patients (more rarely in AdvSM subtypes without an AHN); in at least 70% of these patients, additional somatic mutations are present.[40,41] A poor-risk karyotype (eg, monosomy 7) or complex cytogenetics is observed in association with progression to secondary MCL, but even more strikingly in secondary AML.[40] Because a poor-risk karyotype is an independent prognostic factor in AdvSM, cytogenetic analyses should be routinely performed in addition to *KIT* D816V and NGS in all patients with AdvSM to assess response and clonal evolution as a marker of progression.

Symptoms and quality of life

Regulatory agencies are increasingly incorporating patient-reported outcomes (PROs) evaluating symptom burden and quality of life (QoL) as key measures of clinical benefit during the drug approval process. In a related disease space, the MPN-symptom assessment form (MPN-SAF) and an abridged 10-symptom total symptom score, and the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire core model (QLQ-C30) were used by the FDA and EMA in the approval of JAK inhibitors in myelofibrosis.[42,43]

In the global midostaurin trial,[14] the Memorial Symptom Assessment Scale was used to evaluate changes in PROs across 32 symptom domains, and QoL was assessed using the Medical Outcomes Study 12-Item Short-Form Health Survey. The AdvSM-SAF was the first validated PRO designed specifically to assess AdvSM symptoms[44] and was incorporated into the trials of avapritinib. The AdvSM-SAF is a 10-item daily diary that assesses the severity of eight symptoms of AdvSM, including abdominal pain, nausea, vomiting, diarrhea, spots, itching, flushing, and fatigue, over a 24-hour recall period on a 11-point numeric rating scale in which 0 indicates no symptom and 10 indicates worst imaginable symptom, as well as the frequency of two symptoms (vomiting and diarrhea). Symptom scores are grouped into two domains, a gastrointestinal symptom score (GSS) and skin symptom score. A total symptom score (TSS) combines all items except the two frequency items, with all scores computed as 7-day averages.[44] In the phase I EXPLORER trial, reductions from baseline were seen in both the gastrointestinal and skin domains.[15] Treatment with avapritinib also yielded consistent reductions in the patient-reported AdvSM-SAF TSS, which encompassed gastrointestinal and skin symptoms and fatigue.[15] Mean TSS at baseline was 19.1 points ($n = 40$). Statistically significant improvements in symptoms occurred rapidly and were sustained through cycle 11. At baseline, approximately one-third of patients overall (29 patients; 34%) were using corticosteroids.[15] After baseline, as a result of improvement in SM-associated symptoms, 19 patients (66%) modified corticosteroid use, 12 of whom discontinued corticosteroid use entirely (41%), whereas another seven (24%) were able to reduce the dose.[15]

In the phase II PATHFINDER trial,[16] patients' baseline QoL was negatively affected by disease. Pretreatment mean EORTC−QLQ−C30−QoL score was only 37.8 (range, 0-100, in which 0 represents the lowest QoL and 100 the highest). Mean and median Patient Global Impression of Symptom Severity scores were 2.6 and 3.0, respectively (in which 0 represents no symptoms, and 4 very severe symptoms).[16] The AdvSM-SAF showed that fatigue, abdominal pain, and spots were the most severe symptoms. Mean TSS was 18.3, which was the sum of eight possible common symptoms (each scored 0 to 10, in which 0 represents no symptoms and 10 was the worst imaginable symptoms).

Patient-reported symptoms, as measured by TSS score, improved rapidly after treatment initiation, decreasing by 7.1 points from baseline at cycle 3 (n = 51) and by 9.8 points from baseline at treatment cycle 11 (n = 22; $P < .001$).[16] Mean symptom scores were lower than baseline at cycles 3 and 11 for all SM symptoms, including fatigue, abdominal pain, spots, itching, flushing, nausea, diarrhea, and vomiting. Mean and median Patient Global Impression of Symptom Severity scores improved to 1.6 and 2.0, respectively (moderate symptoms that are difficult to ignore) by cycle 3 and to 1.2 and 1.0, respectively (minimal symptoms that are easy to ignore) by cycle 11. Although no data are available from the avapritinib trials to establish whether the drug can reduce rates of anaphylaxis, one case report found that refractory anaphylaxis was aborted by avapritinib.[45]

EVOLUTION OF AdvSM RESPONSE CRITERIA

Response criteria for AdvSM have evolved in tandem with the development of AdvSM-directed therapies, particularly *KIT*-targeting agents (Figure 1). In 2003, the Valent response criteria established a basic foundation for quantifying treatment effects on measures of MC burden and C-findings (Table I).[46] Although the Valent response criteria included quantifiable changes in BM MC burden and serum tryptase level to define the remission subtypes of major response, the minimal improvements in laboratory C-findings are not defined and required only that they improve from the abnormal to the normal reference range. Therefore, if minimally abnormal baseline C-findings are found to resolve with treatment, the true clinical benefit of such modest changes may be questionable and overestimated. In addition, the Valent response criteria do not define red blood cell or platelet transfusion dependence or any criteria for transfusion independence.

Case reports and case series evaluating interferon-alfa, cladribine, hydroxyurea, and tyrosine kinase inhibitors (eg, imatinib, dasatinib, and nilotinib) employed Valent response criteria or their various modifications.[53-59] However, the small numbers of patients and clinically heterogeneous subtypes studied, the lack of granular response data, and the shortcomings of the Valent response criteria made it challenging to draw broad conclusions about the clinical benefit of these agents in patients with AdvSM.

In 2010, the Mayo Clinic generated response criteria for AdvSM based on (1) disease-related symptoms, (2) organomegaly/lymphadenopathy, (3) organ damage (referred to as disease-related organopathy), and (4) BM findings (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).[47] Response categories of CR, major response, PR, SD, and progressive disease were based on resolution or improvement, or worsening in one or more of these categories. A useful concept to come from the Mayo Clinic criteria was the identification of a minimal grade of organ damage to be considered clinically relevant and eligible for response adjudication, (eg, grade 2 or

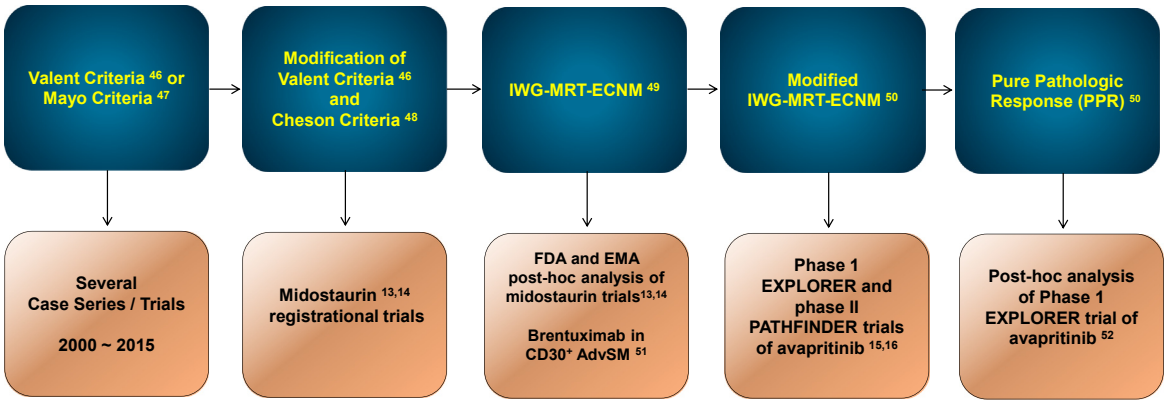

FIGURE 1. Evolution of response criteria in advanced systemic mastocytosis (AdvSM) over the past 2 decades with examples of their application to clinical trials. *EMA*, European Medicines Agency; *FDA*, US Food and Drug Administration; *IWG-MRT-ECNM*, International Working-Group for Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis.

TABLE I. Valent response criteria in aggressive systemic mastocytosis and mast cell leukemia

Major response
1. Complete resolution of at least one C-finding and no progression in other C-findings
2. Complete remission: disappearance of mast cell infiltrates in affected organs, decrease of serum tryptase to <20 ng/mL, and disappearance of systemic mastocytosis–associated organomegaly
3. Incomplete remission: decrease in mast cell infiltrates in affected organs and/or substantial decrease of serum tryptase level, and/or visible regression of organomegaly
4. Pure clinical response: without decrease in mast cell infiltrates, without decrease in tryptase levels, and without regression of organomegaly
Partial response
Incomplete regression of one or more C-finding,* without complete regression, and no progression in other C-findings
1. Good partial response: >50% regression
2. Minor response: ≤50% regression
No response
C-finding(s) persistent or progressive†
1. Stable disease: C-finding parameters show constant range
2. Progressive disease: one or more C-findings show progression

*With or without decrease in mast cell infiltrates, serum tryptase levels, and organomegaly.
†In case of progressive C-findings and documented response in other C-findings, the final diagnosis is still progressive disease.

higher based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03[60]).

Recognizing some challenges of the Valent response criteria, the global trial of midostaurin, which enrolled patients from 2009 to 2013,[14] adopted modified Valent response criteria that specified minimal criteria of improvement for all C-findings and incorporated modified Cheson response criteria[48] (created for MDS) for red blood cell and platelet transfusions.

The next iteration of response criteria for AdvSM, the International Working-Group for Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis, was published in 2013.[49] Referred to as the IWG criteria (Table II), their intent was to establish more stringent, well-defined, and more clinically relevant definitions for eligible SM-related organ damage and response for AdvSM patients enrolled in clinical trials. Clinical improvement defines the resolution of one or more eligible organ damage findings, which is a minimal requirement for all higher-level responses. A PR also requires 50% or greater improvement in serum tryptase level and BM MC burden, whereas a CR requires the elimination of BM MC aggregates, improvement in the serum tryptase level to 20 ng/mL or less, resolution of all baseline organ damage findings, and resolution of hepatosplenomegaly. All responses must endure for 12 weeks. Criteria for progressive disease and loss of response (LOR) are detailed in the publication.[49] In the phase I EXPLORER and phase II PATHFINDER trials of avapritinib,[15,16] modifications of the IWG criteria were used to adjudicate responses.[50] Table II lists differences between the two criteria. With IWG criteria, splenomegaly is defined as greater than 5 cm and symptomatic; with mIWG criteria, the organ damage finding of splenomegaly is defined as 5 cm or greater and there is no symptom requirement. The category of CRh (CR with partial hematologic recovery) was added and is defined by the criteria of an absolute neutrophil count of 0.5×10^9/L or greater, a hemoglobin value of 8 g/dL or greater, and a platelet count of 50×10^9/L or greater. The addition of the CRh category reflects the fact that non-SM factors contribute to cytopenias, such as drug-related myelosuppression and/or the AHN component.

REAL-WORLD CHALLENGES OF APPLYING AdvSM RESPONSE CRITERIA

Several disease factors render response assessment in AdvSM complex and difficult. This is relevant to the adjudication of patients on clinical trials as well as for practicing physicians. In most patients, AdvSM is a multimutated stem cell disorder affecting multiple cell lineages. The response to KIT inhibitors may be variable among the clinical parameters used to examine the MC compartment (eg, BM MC infiltration and serum tryptase), the non-MC/AHN compartment (eg, monocytes, eosinophils, and blasts) as well as findings that can reflect both compartments (eg, anemia, thrombocytopenia, splenomegaly, gastrointestinal tract/liver, and *KIT* D816V VAF).[7,13-16] Whereas a reduction in BM MC infiltration and serum tryptase is closely associated with a response within the MC compartment, findings associated with

TABLE II. International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (IWG-MRT-ECNM) and modified IWG-MRT-ECNM definitions of evaluable organ damage and response[49,50]

	IWG-MRT-ECNM definition	IWG-MRT-ECNM response criteria	Modified IWG-MRT-ECNM response criteria
Nonhematologic organ damage			
Ascites or pleural effusions	Symptomatic ascites or pleural effusion requiring medical intervention such as use of diuretics (grade 2) or two or more therapeutic paracenteses or thoracenteses (grade 3) at least 28 d apart over 12 wk before start of treatment with one procedure performed 6 wk before start of treatment	Complete resolution of symptomatic ascites or pleural effusion (including trace/minimal on radiographic imaging) and no further need for diuretics for ≥12 wk and no further need for diuretics for ≥12 wk or no therapeutic paracenteses or thoracentesis for ≥12 wk	Same as IWG-MRT-ECNM
Liver function abnormalities	Grade 2 or greater abnormalities in direct bilirubin (>1.5 × ULN), AST (>3.0 × ULN), ALT (>3.0 × ULN), or ALP (>2.5 × ULN) in the presence of ascites and/or clinically relevant portal hypertension, and/or liver MC infiltration that is biopsy-proven or no other identified cause of abnormal liver function	Reversion of one or more LFTs to normal range for ≥12 wk	Same as IWG-MRT-ECNM
Hypoalbuminemia	Grade 2 or greater hypoalbuminemia (<3.0 g/dL)	Reversion of albumin to normal range for ≥12 wk	Same as IWG-MRT-ECNM
Marked symptomatic splenomegaly	Spleen that is palpable >5 cm below left costal margin and patient endorses symptoms of discomfort and/or early satiety	≥50% reduction in palpable splenomegaly (or ≥35% reduction in spleen volume based on 3D MRI or CT scan) and no endorsement of discomfort and/or early satiety for ≥12 wk	Definition: symptomatic or nonsymptomatic splenomegaly palpable ≥5 cm below left costal margin. Response criteria: ≥35% reduction in spleen volume based on 3D MRI or CT scan for ≥12 wk
Weight loss	N/A	N/A	Definition: medically documented >10% weight loss in past 24 wk (±12 wk) Response criteria: reversion of >50% of weight loss in 24 wk preceding treatment
Hematologic organ damage			
Neutropenia	Grade 3 or greater ANC (<1.0 × 10^9/L)	≥100% increase and absolute increase ≥0.5 × 10^9/L for ≥12 wk	Same as IWG-MRT-ECNM with allowance of CRh*
Anemia (transfusion-independent)	Grade 2 or greater Hgb (<10 g/dL)	An increase in Hgb ≥2 g/dL that is maintained for ≥12 wk	Same as IWG-MRT-ECNM with allowance of CRh*
Anemia (transfusion-dependent)	Transfusion of ≥6 units of PRBCs in 12 wk before start of treatment and most recent transfusion occurring during 4 wk before start of treatment and transfusions administered for Hgb ≤8.5 g/dL and reason for transfusions is not bleeding, hemolysis, or therapy-related	Transfusion independence for ≥12 wk and maintenance of Hgb ≥8.5 g/dL at end of 12-wk period of response duration	Same as IWG-MRT-ECNM with allowance of CRh*

(continued)

TABLE II. *(Continued)*

	IWG-MRT-ECNM definition	IWG-MRT-ECNM response criteria	Modified IWG-MRT-ECNM response criteria
Thrombocytopenia (transfusion-independent)	Grade 2 or greater thrombocytopenia (<75 × 10^9/L)	≥100% increase and absolute increase ≥50 × 10^9/L and no need for platelet transfusion for ≥12 wk	Same as IWG-MRT-ECNM with allowance of CRh*
Thrombocytopenia (transfusion-dependent)	Transfusion of ≥6 units of apheresed platelets during 12 wk preceding treatment and ≥2 units transfused during 4 wk preceding treatment and transfusions administered for platelet count <20 × 10^9/L	Transfusion independence for ≥12 wk and maintenance of platelet count ≥20 × 10^9/L	Same as IWG-MRT-ECNM with allowance of CRh*

3D MRI, three-dimensional magnetic resonance imaging; *ALP*, alkaline phosphatase; *ALT*, alanine aminotransferase; *ANC*, absolute neutrophil count; *AST*, aspartate aminotransferase; *CRh*, complete remission with partial hematologic recovery; *CT*, computed tomography; *Hgb*, hemoglobin; *LFT*, liver function test; *MC*, mast cell; *N/A*, not applicable; *PBRC*, packed red blood cell; *ULN*, upper limit of normal.
*Complete remission with partial hematologic recovery requires minimum levels for peripheral blood counts: absolute neutrophil count of ≥0.5 × 10^9/L with normal differential (absence of neoplastic mast cells and blasts < 1%) and platelet count of ≥50 × 10^9/L and hemoglobin count of ≥8.0 g/dL. The grade is based on the Common Terminology Criteria for Adverse Events, version 4.03.[60]

organ damage (eg, cytopenias, liver dysfunction, palpable splenomegaly with hypersplenism, hypoalbuminemia, malabsorption with weight loss, ascites, pleural effusions, and large osteolysis [eg, greater than 2 cm] with or without pathologic fractures) cannot always be confidently assigned to the SM or AHN disease component. In some cases, organ-directed biopsy may be indicated to establish whether the SM or AHN component, or both, contribute to organ damage. However, the clinical imperative of such invasive procedures must be weighed against their safety, because bleeding or other complications may develop in AdvSM patients. Moreover, measurement of several C-findings lacks precision (eg, splenomegaly or ascites/effusions, and lytic bone lesions).[49] In addition, although weight loss is common in AdvSM, it is subject to several challenges that make it a suboptimal organ damage finding for adjudication.[49] For example, accurate estimation of weight loss can be confounded by the accumulation of third-space fluid (eg, ascites or pleural effusion). Moreover, the use of diuretics or paracentesis or thoracentesis can cause significant fluid shifts. Formal medical documentation of weight loss over a specified period (eg, greater than 10% over the 6-month pretrial period) is often missing, limiting the usefulness of this criterion for clinical trials. However, patient self-reporting of weight loss can be a useful clinical end point for practitioners to follow when initiating *KIT* inhibitors or other SM treatment. Despite these caveats, medically documented weight loss is included as eligible organ damage in mIWG criteria and can be useful to enroll patients in trials in the absence of other C-findings if they are required for trial eligibility.

Lingering cytopenias, and in some cases nonhematologic organ damage, can reflect prior therapy, making the evaluation of what is truly SM-related organ damage difficult. Similarly, during therapy, emergent or progressive cytopenias may reflect drug toxicity. The distinction between SM- and AHN-associated cytopenias is similarly challenging. AHN—related cytopenias may hinder the development of hematologic responses to KIT-targeted therapy. To dissect whether worsening hematologic and/or nonhematologic organ damage is related to the SM or AHN component, serial tracking of objective measures of MC burden (BM MC percentage and serum tryptase level) may help distinguish whether progressive hematologic or nonhematologic organ damage is SM-related or caused by other factors such as the AHN, drug toxicity, or comorbid conditions (eg, gastrointestinal bleeding as a cause of worsening anemia and/or need for red blood cell transfusions). Such clinical conundrums are common in the context of clinical trials and reflect challenges commonly encountered in clinical practice.

FEEDBACK FROM REGULATORY AUTHORITIES

By IWG criteria, the overall response rate (ORR) is defined as CR + PR + CI. Whereas the EMA accepted this definition of response in their *post hoc* analysis of the global midostaurin registrational trial, in which the 28% ORR was defined by CR + PR + CI (1% + 15% + 12%), the FDA defined a 17% *post hoc* ORR by CR + PR only (2% + 15%).[49,61,62] This decision may have reflected several concerns, including (1) uncertainty about whether CI represented a positive impact on the SM or AHN component, or some combination of both; and (2) whether changes in various laboratory findings that define CI were sufficiently representative of clinical benefit. Indeed, it is not well-understood whether normalization of one or more organ

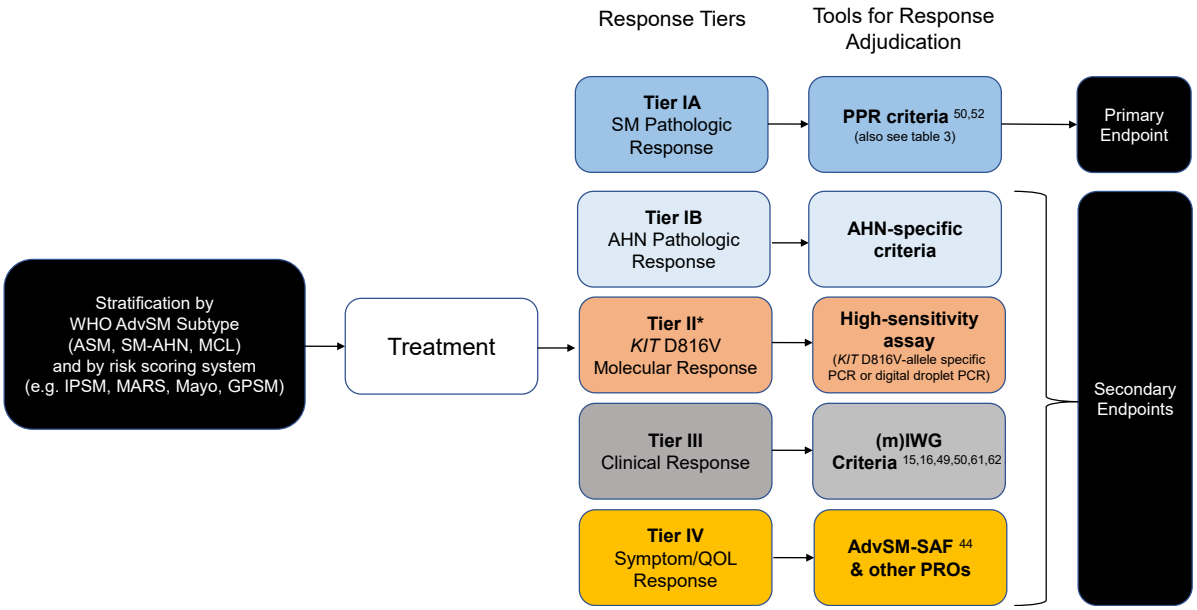

FIGURE 2. Proposed ECNM–AIM response criteria for AdvSM. Tiers IA and 1B consist of histopathologic response in the systemic mastocytosis (SM) and associated hematologic neoplasm (AHN) components, respectively. Tier II is composed of the *KIT* D816V molecular response.* Tier III consists of an evaluation of clinical organ damage using International Working Group (IWG) or modified IWG criteria. Tier IV is symptom/quality of life (QoL) response using patient-reported outcome instruments (PROs) that are validated in advanced systemic mastocytosis (AdvSM) (eg, the AdvSM assessment form [AdvSM-SAF] as well as other generalizable PROs that may be used to measure mastocytosis symptoms and QoL. *Tier II includes an evaluation of standard karyotype and dynamic changes in myeloid mutation profile by next-generation sequencing. *GPSM*, Global Prognostic Score for Mastocytosis; *IPSM*, International Prognostic Scoring System for Mastocytosis; *MARS*, mutation-adjusted risk score; *MCL*, mast cell leukemia; *OS*, overall survival; *PCR*, polymerase chain reaction; *PFS*, progression-free overall survival; *PPR*, pure pathologic response; *WHO*, World Health Organization.

damage findings is a surrogate marker for important clinical outcomes such as progression-free and OS. However, histopathologic response, measured by achievement of a PR or CR (or CRh) reflects a reduction in objective measures of MC burden (eg, BM MC percentage and serum tryptase level) and is considered by regulatory health authorities to be a more compelling surrogate of long-term clinical benefit.

PURE PATHOLOGIC RESPONSE CRITERIA

In part because of the increased complexity of mIWG criteria, the focus on histopathologic response by the regulatory authorities, and the challenges of interpreting the value of CI in organ damage, focus has increasing on the development of response criteria anchored by objective measures of MC burden. Additional justification for focusing on histopathologic response arose during the central response adjudication of the midostaurin and avapritinib trials. In some cases, we noted that lingering C-findings (possibly owing to AHN, drug toxicity, or irreversible organ damage by prior neoplastic MC infiltration) resulted in downgrading of responses despite complete or partial (eg, 50% or greater) elimination of MC aggregates. In addition, an unmet need exists for more simplified response criteria that are accessible to practitioners outside the context of clinical trials.

To address these issues, pure pathologic response (PPR) criteria were created.[50,52] Pure pathologic response consists of quantitative assessment of BM MC infiltration, serum tryptase level, and complete or partial hematologic response. Complete remission is defined as the absence of BM MC aggregates and serum tryptase less than 20 ng/mL with full or partial (CRh) hematologic recovery; PR is defined by a 50% or greater reduction in BM MC infiltration and serum tryptase level.

Pure pathologic response criteria were evaluated on a *post hoc* basis in the phase I trial EXPLORER trial of avapritinib.[52] Among 53 evaluable AdvSM patients, the ORR per mIWG and PPR were respectively 75% and 77%. According to mIWG and PPR criteria, corresponding rates of CR/CRh/PR were 15%, 21%, 34%, and 23%, 24%, and 30%, respectively, and the CI rate was 6% with mIWG (not applicable to PPR). Although there was a similar ORR, there was a higher CR/CRh rate by PPR compared with mIWG, demonstrating discordance between pathologic and clinical responses. In addition, 11 additional AdvSM patients lacking evaluable mIWG organ damage findings at baseline were evaluable by PPR: three CR, three CRh, three PR, and two SD. Notably, using a landmark analysis starting at the end of cycle 6, PPR was significantly associated with improved OS when comparing responders (CR/CRh and PR) and nonresponders (SD) ($P = .013$). In contrast, differences in OS did not reach statistical significance when classifying response by mIWG criteria using the same landmark analysis. Because a primary purpose of response criteria is to serve as a surrogate of long-term clinical benefit, including OS, PPR may be particularly useful in demonstrating how SM-directed therapies affect disease natural history. It remains unclear whether these findings relate only to avapritinib and other *KIT* D816V inhibitors, or to other SM therapies as well.

TABLE III. Definitions for tiers of response according to proposed ECNM–AIM response criteria*

Response category†	Definition of response
Tier IA: SM pathologic response	
CR or CRh‡	BM MC aggregates eliminated and serum tryptase <20 ng/mL§,‖
Partial remission	≥50% reduction in BM MCs and serum tryptase
Stable disease	Not in CR, PR, or PD
PD	Transformation to secondary AML or MCL (if baseline diagnosis is ASM or SM-AHN)
Loss of response	Return of BM MC burden and serum tryptase values to baseline values or higher¶
Tier IB: AHN pathologic response	AHN histopathologic response is adjudicated according to AHN-specific response criteria for relevant myeloid neoplasm
Tier II: *KIT* D816V molecular response#	
Complete molecular response	*KIT* D816V mutant allele frequency falls below limit of detection by high-sensitivity assay**
Partial molecular response	≥50% reduction in *KIT* D816V mutant allele frequency (but still detectable)
Tier II: Cytogenetic response#	
Complete cytogenetic response	No evidence of baseline cytogenetic abnormality on standard karyotyping with minimum of 20 metaphases or 0% of nuclei by FISH on BM sample (or not exceeding normal cutoff of probe). FISH and cytogenetics from PB are acceptable if marrow sample is inadequate
Partial cytogenetic response	≥50% reduction of baseline cytogenetic abnormality on standard karyotyping with minimum of 20 metaphases or ≥50% reduction of positive nuclei by FISH on marrow sample. FISH and cytogenetics from PB are acceptable if marrow sample is inadequate
Tier III: Clinical response	Clinical improvement in organ damage is adjudicated according to original[49] or modified IWG criteria[15,16,50]
Tier IV: Symptom/QoL response	Symptom scores and/or QoL may be adjudicated using Advanced Systemic Mastocytosis Symptom Assessment Form[44] or other patient-reported outcome instruments such as European Organization for Research and Treatment of Cancer-QLQ-C30 or patient global impression of change.

AHN, associated hematologic neoplasm; *AML*, acute myeloid leukemia; *ASM*, aggressive systemic mastocytosis; *BM*, bone marrow; *CR*, complete remission; *CRh*, complete remission with partial hematologic recovery; *FISH*, fluorescence *in situ* hybridization; *IWG*, International Working Group; *MC*, mast cell; *PB*, peripheral blood; *PCR*, polymerase chain reaction; *PD*, progressive disease; *PR*, partial remission; *QoL*, quality of life; SM, systemic mastocytosis.

*Relevant changes in pathologic response of SM and AHN components should be described and documented accordingly during treatment: for example, CR of ASM and PD in AHN (transformation from myelodysplastic syndrome to AML).

†Responses must endure for ≥12 wk.

‡Complete remission (CR) and CRh are defined by modified IWG criteria: a baseline tryptase value of 40 ng/mL or greater is required for response adjudication. In patients with a confirmed diagnosis of HαT who have achieved elimination of BM MC aggregates (and with a serum tryptase level greater than or less than 20 ng/mL, a CR or CRh may still be assigned. In these cases, the CR or CRh designation should be denoted by superscript HαT (eg, $CR^{H\alpha T}$).

§Bone marrow (BM) MC burden should be evaluated on a core biopsy with immunohistochemistry using a combination of tryptase, CD117, and CD25. Scattered interstitial mast cells are permitted with assignment of CR/CRh (in these cases, BM MC burden should be <5%). In patients with complete elimination of BM MC aggregates but without a decrease in tryptase less than 20 ng/mL, evaluation for hereditary α-tryptasemia can be considered.

‖If SM-related organ damage is suspected in an organ besides the BM, organ-directed biopsy is recommended before treatment when feasible and safe. Similarly, a repeat on-treatment organ-directed biopsy may be considered, but SM pathologic response is based solely on the BM, not on other extracutaneous organ responses. However, pathologic responses in these other organs should be recorded.

¶Loss of response should be confirmed after 4 wk when clinically feasible.

#If new mutations in *KIT* or other than *KIT* develop upon treatment, these should be recorded. Similarly, new clonal abnormalities detected upon standard karyotyping should be documented.

**High-sensitivity assays such as *KIT* D816V allele-specific PCR or digital droplet PCR should be used. Bone marrow as a tissue source is preferred over PB.

PROPOSED ECNM–AIM RESPONSE CRITERIA

Several single variables or groups of parameters are available for the establishment of response criteria: (1) BM MC infiltration; (2) serum tryptase level; (3) C-findings; (4) *KIT* D816V VAF/EAB; (5) monocytes, eosinophils, and/or blasts in PB; and (6) symptoms or QOL. Given the increasing focus on pathologic response, preliminary evidence of its correlation with long-term outcomes, and the challenges of interpreting C-findings, we have proposed response criteria based on a modular approach in which these parameters are uncoupled from each other and evaluated in a tiered approach.[50]

Tier IA is dedicated to a SM pathologic response that includes assessing BM MC infiltration, serum tryptase level, and complete blood count with differential using the same criteria as PPR. If an AHN is present, this component should be evaluated in tier IB, separate from, but in parallel with, tier IA, with AHN-specific response criteria. If elevated, monocytes/eosinophils/blasts are the purest representatives of AHN, and their response should be considered as part of these AHN criteria.

KIT D816V molecular response by a high-sensitivity assay such as *KIT* D816V allele-specific reverse-transcriptase PCR or ddPCR is considered to be tier II of response. As demonstrated in the phase I EXPLORER trial of avapritinib,[15] molecular remission of *KIT* D816V using a high-sensitivity assay appears to be enriched in patients achieving a CR or CRh versus PR. Assay-specific differences of the LOD and sample-specific differences of the reachable sensitivity (eg, copies of the reference gene or total number of *KIT* copies) may influence the result of a complete molecular remission. A definition of reporting standards for molecular response levels of *KIT* D816V may improve the

TABLE IV. Features of advanced systemic mastocytosis response criteria

Feature of response criteria	Valent	Mayo	IWG-MRT-ECNM	Modified IWG-MRT-ECNM	Pure pathologic response	ECNM–AIM
Specificity in defining hematologic and nonhematologic C-findings and definitions of response	+	++	++++	++++	Not applicable	++++
Requires C-findings to adjudicate response	Yes	Yes*	Yes†	Yes†	No	No
Distinguishes complete remission vs complete remission with partial hematologic recovery	No	No	No	Yes	Yes	Yes
KIT D816V molecular response	No	Yes‡	No	No	Yes	Yes
Addresses associated hematologic neoplasm	No	No	Yes	Yes	No	Yes
Addresses symptoms	No	Yes	No	No	No	Yes
Used by regulatory authorities	No	No	Yes	Yes	TBD	TBD
Applicability for clinical trials	+	++	+++	+++	+++	++++
Ease of use in clinical practice	++	++	+	+	++++	+++

+, minimally featured; ++++, highly featured; *IWG-MRT-ECNM*, International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; *TBD*, to be determined.
*Pure pathologic response definition does not always require resolution of disease-related organopathy.
†In cases of mast cell leukemia, lack of C-findings is permitted for response adjudication.
‡Bone marrow findings (response category D) include assessment of *KIT* D816V status.

informative value of molecular minimal residual disease assessment in the future.[63]

Besides *KIT* D816V analysis, standard karyotyping and serial evaluation of the mutational landscape of AdvSM by NGS myeloid mutation panels should be included in tier II response. NGS is considered critical for the dynamic assessment of clonal hierarchy during *KIT* inhibitor therapy or other therapies. Thus far, in the midostaurin and avapritinib trials, there were no consistent or recurrent patterns of mutations as a basis of resistance. As mentioned, in some cases there was an increase in the VAF/EAB of *KIT* D816V, and in other cases new mutations emerged, or an increase in the VAF of baseline mutations in other genes besides *KIT* D816V was noted. In an analysis of avapritinib-treated patients in the EXPLORER trial, there was no discernible difference in mutation patterns in patients with or without clinical progression.[64] To date, no *KIT* mutations besides D816V have been uncovered as a basis for resistance. In cases with *KIT* mutations other than *KIT* D816V, which are present in a small fraction of all AdvSM patients (less than 5%), molecular assays with high sensitivity similar to those currently available for *KIT* D816V need to be developed.

Tier III response would use IWG or mIWG criteria to adjudicate clinical responses (eg, CI in eligible organ damage). Tier IV consists of symptom and QoL response, and can employ PRO instruments including the AdvSM-SAF and other more generalized PRO tools such as the EORTC-QLQ-C30, and patient global impression of change. Currently, there is no one standard PRO for evaluating AdvSM symptom burden and QoL. Hereditary α-tryptasemia, which has been found in 10% to 17% of SM patients, including a smaller fraction (10%) of AdvSM patients, may complicate assessment and interpretation of symptom burden (as well as serum tryptase levels).[65-68]

Potential advantages of proposed ECNM–AIM response criteria

The use of BM MC burden, serum tryptase level, and blood counts, which comprise the tier IA SM pathologic response, are widely available and easily interpretable by practicing physicians to determine treatment response. The advantage of these criteria is that these simple and objective markers are uncoupled from C-finding assessments, which can be complicated by the AHN, treatment toxicity, or patient comorbidities. In addition, they are applicable to all AdvSM patients with measurable disease burden, regardless of the presence of C-findings.

In clinical practice, the tier IA SM pathologic response would be synonymous with best treatment response. However, we also encourage reporting of the AHN pathologic response, when relevant (tier IB), as well as changes in the *KIT* D816V VAF using a high-sensitivity assay (tier II), changes in C-findings (tier III), and symptoms or QOL (tier IV). Reporting of all tiers of response provides a more granular and composite picture of clinical benefit. One concern is that there may be the tendency in clinical practice to focus exclusively on SM pathologic response and to ignore the other tiers of response. However, the treatment goals of some patients and their physicians may be more aligned with improving organ damage and symptoms or QOL more so than changes in objective measures of MC burden. This tiered approach therefore also allows an *à la carte* approach, focusing on response categories that reflect the needs of individual patients.

In the context of clinical trials, tier IA SM pathologic response would be used for the primary end point, and tiers IB, II, III, and

IV would serve as secondary end points. Additional secondary end points include time to initial SM pathologic response and duration of response. Pretreatment variables and each tier of response could be assessed in a multivariable analysis to gauge their impact on event-free, progression-free, and OS (Figure 2). Table III provides detailed definitions of SM pathologic response applied from PPR criteria, as well as definitions for molecular and cytogenetic responses. Uncoupling SM pathologic response from tiers IB and III attempts to address regulatory authorities' concerns about the confounding effects of an AHN and removes SM-related organ damage from the calculus of the primary end point given concerns regarding whether improvement in C-findings contributes to long-term clinical benefit. The separation of SM pathologic response from clinical response also eliminates concerns regarding lingering C-findings downgrading a CR or PR to SD because of their requirement for the resolution of one or more C-findings. Table IV lists the comparative features of the proposed ECNM−AIM response criteria versus prior response criteria.

CONCLUSION

The registrational trials of midostaurin and avapritinib, which included central adjudication of histopathologic and clinical responses, have provided an unprecedented opportunity to evaluate the difficulties of response criteria in AdvSM. To a large extent, the challenges with response criteria reflect the difficulty of capturing the complexity of AdvSM. The proposed ECNM−AIM response criteria, born from successive prior versions, use a tiered approach to uncouple the effects of histopathologic, molecular, clinical, and symptom response on long-term outcomes. The achievement of molecular responses of *KIT* D816V, a new response benchmark, provides an opportunity to apply the concept of minimal residual disease to AdvSM, similar to its use in other hematolymphoid neoplasms.

These newly proposed criteria require evaluation in prospective future clinical trials of selective *KIT* inhibitors and other novel agents. In addition to the use of these refined response criteria, another important consideration is the employment of prognostic scoring systems (eg, mutation-adjusted risk score, Mayo Alliance Prognostic System for Mastocytosis, IPSM, Global Prognostic Score for Mastocytosis) to optimize pretreatment stratification of patients enrolled in clinical trials.[20-23] Finally, it is hoped that incorporating novel biomarkers, such as single-cell genome sequencing of cells derived from SM and AHN cell lineage compartments,[69] may provide useful correlative information about drug efficacy and mechanisms of resistance. In turn, these biological-clinical correlative data may further inform future proposals for response criteria in both advanced and non-advanced forms of SM.

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TABLE E1. Mayo Clinic revised response criteria in aggressive systemic mastocytosis

Response category	Disease-related symptoms* (A)	Organomegaly/ lymphadenopathy† (B)	Disease-related organopathy‡ (C)	BM findings§ (D)
CR: A + B + C + D required (when present)	Complete resolution for 3 mo	Complete resolution†	Complete resolution‖	Absence of abnormal MC infiltration¶
Major response: A + B + C + D required (when present)	No progression (at a minimum)	No progression (at a minimum)	Complete resolution of at least one element of organopathy‡,#	>50% decrease in BM MC (%)
PR: A or B or C (without progression of others)	Complete resolution for 3 mo	Complete resolution†	Two or more grades improvement in at least one element of organopathy#,**	No progression (at a minimum)
Stable disease	None of the previous responses			
Progressive disease: B or C required	Not applicable††	>50% increase from baseline†	Two or more grades worsening from baseline	Not applicable

BM, bone marrow; CR, complete response; MC, mast cell; PR, partial response

Responses are validated only if they last for no fewer than 4 wk. The correlation between clinical response and change in MC mediator level(s)‡‡ and *KIT* D816V allele burden needs further study. The authors recommend prospective sample collection before treatment and at the time of peak clinical response for comparison.

*To be considered a parameter for response measurement, symptoms must be frequent (occurring at least once per month), severe enough to require treatment despite prophylaxis (H1 and H2 histamine receptor antagonists, proton pump inhibitors, and/or oral cromolyn sodium), and accompanied by either organomegaly/lymphadenopathy or organopathy.

†Palpable disease or measurable disease by imaging studies are required at baseline. Baseline and posttreatment status must be documented by imaging studies to allow third-party confirmation of response or progression.

‡Grade 2 or greater ascites (not optimally controlled with medical therapy) or grade 2 or greater weight loss or grade 2 or greater osteoporosis (large osteolytic lesions or pathologic fracture) or grade 2 or greater anemia (hemoglobin value <10 g/dL) or thrombocytopenia (platelet count $<75 \times 10^9$/L) or ≥ grade 2 hyperbilirubinemia or hypoalbuminemia that is a disease-related change from baseline (grades are per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03[60]).

§Bone marrow characteristics to be described: (1) BM MC burden (percentage) based on tryptase/CD117 (*KIT*) immunostaining, (2) cytogenetics, and (3) *KIT* D816V status.

‖Complete resolution of all evidence of organopathy unless observed changes are deemed related to treatment.

¶Cytogenetic remission is not required. Cytogenetic response, if any, to be documented as: CR disappearance of previously documented chromosomal abnormality without appearance of new ones, and PR at least 50% reduction of cytogenetic abnormality.

#No progression in other elements of organopathy should be evident unless observed changes are deemed related to treatment.

**Per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[60]

††Given the difficulty of distinguishing treatment-related symptoms from disease-related symptoms.

‡‡Serum tryptase, 24-h urine histamine, methylhistamine, and β-prostaglandin F2α.