Special Article

European Competence Network on Mastocytosis (ECNM): 20-Year Jubilee, Updates, and Future Perspectives

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In 2002, the European Competence Network on Mastocytosis (ECNM) was launched as a multidisciplinary collaborative initiative to increase the awareness and to improve diagnosis and management of patients with mast cell (MC) disorders. The ECNM consists of a net of specialized centers, expert physicians, and scientists who dedicate their work to MC diseases. One essential aim of the ECNM is to timely distribute all available information about the disease to patients, doctors, and scientists. In the past 20 years, the ECNM has expanded substantially and contributed successfully to the development of new diagnostic concepts, and to the classification, prognostication, and treatments of patients with mastocytosis and MC activation disorders. The ECNM also organized annual meetings and several working conferences, thereby supporting the

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Abbreviations used
AIM- American Initiative in Mast Cell Diseases
ASM- Aggressive systemic mastocytosis
CM- Cutaneous mastocytosis
ECNM- European Competence Network on Mastocytosis
MC- Mast cell(s)
MCAS- Mast cell activation syndrome
MCL- Mast cell leukemia
OIS- Open innovation in science
ROY- Researcher of the Year
SM- Systemic mastocytosis
WHO- World Health Organization

development of the World Health Organization classification between 2002 and 2022. In addition, the ECNM established a robust and rapidly expanding patient registry and supported the development of new prognostic scoring systems and new treatment approaches. In all projects, ECNM representatives collaborated closely with their U.S. colleagues, various patient organizations, and other scientific networks. Finally, ECNM members have started several collaborations with industrial partners, leading to the preclinical development and clinical testing of KIT-targeting drugs in systemic mastocytosis, and some of these drugs received licensing approval in recent years. All these networking activities and collaborations have strengthened the ECNM and supported our efforts to increase awareness of MC disorders and to improve diagnosis, prognostication, and therapy in patients. **(J Allergy Clin Immunol Pract 2023;11:1706-17)**

Key words: *Mast cells; Mastocytosis; Mast cell activation disorders; MCAS; ECNM*

INTRODUCTION

Mastocytosis is a heterogeneous group of hematopoietic neoplasms characterized by an abnormal expansion and accumulation of tissue mast cells (MC) in certain organ systems, including the skin, bone marrow, and other internal organs.[1-9] Based on the organ system(s) involved, mastocytosis can be divided into cutaneous mastocytosis (CM), systemic mastocytosis (SM), and localized MC tumors.[1,3-6,8-12] According to the classification of the World Health Organization (WHO), several variants of CM and SM are recognized.[11-18] The WHO classification splits SM into bone marrow mastocytosis, indolent SM, smoldering SM, aggressive SM (ASM), SM with an associated hematological neoplasm (SM-AHN), and MC leukemia (MCL).[11-18] The clinical course, patterns of symptoms, and prognosis vary among patients, depending on the disease variant, molecular features, organ involvement, the presence of an associated hematological neoplasm, and the presence and type of comorbidities, including immunoglobulin E−mediated allergies.[11,12,19-28] ASM, SM-AHN, and MCL are collectively termed advanced SM because these categories share a poor prognosis.[11-18]

Independent of the (sub)variant of CM or SM, patients may present with mediator-related symptoms that can be mild, severe, or sometimes even life-threatening.[2-7,23,24,29-32] In those with

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severe anaphylaxis, a MC activation syndrome (MCAS) may be documented.[29-31] Many of these patients suffer from a concomitant, immunoglobulin E–dependent allergy.[24,29-31] Apart from mediator-associated symptoms, patients with MC disorders may also present with osteopathy (often in form of osteopenia or osteoporosis), gastrointestinal symptoms, neurological or psychiatric symptoms, and/or cutaneous lesions and symptoms, such as itching or flushing.[32-40] In advanced SM, additional problems are recorded, such as cytopenia, ascites, malabsorption, lymphadenopathy, splenomegaly, hepatopathy and/or hepatomegaly, or larger (sometimes painful) osteolytic lesions with pathological fractures.[21,22,26-28,41-44] Whereas the prognosis in CM, bone marrow mastocytosis, and indolent SM is excellent, the prognosis concerning overall survival and progression-free survival in advanced SM is unfavorable.[21,22,25-28,41-45]

The classification of mastocytosis stems back to 1949, when a first report of SM was published.[46] Between 1950 and 1970, several distinct entities of SM, including a leukemic variant (MCL), were introduced together with disease-related features.[47,48] A first comprehensive classification was proposed by the Kiel consortium with Karl Lennert in 1979.[1] In 1991, a first consensus classification was proposed by Dean Metcalfe.[5] Between 1990 and 2000, several disease-related or even disease-specific parameters and variables were identified and validated.[49-55] These disease-associated features were discussed and formulated into diagnostic consensus criteria to define CM and SM and to classify SM variants.[56] Final rounds of discussions were organized in the Year 2000 Working Conference on Mastocytosis in Vienna.[11] The resulting consensus criteria and consensus classification were adopted by the WHO in 2001.[13] Between 2001 and 2022, the E.U.-U.S. consensus group continued to work on specific markers and standards to improve diagnosis and prognostication in CM and SM, to update and refine diagnostic criteria and the WHO classification, and to formulate treatment response criteria.[1-15,17,27-30] In 2002, the European group decided that it would be desirable to establish a Competence Network for Mastocytosis in Europe. This network, termed the European Competence Network on Mastocytosis (ECNM), was inaugurated and launched in 2002.[57-59] In this article, the accomplishments of the ECNM, the current status of the network, and primary goals and perspectives for the future are presented and new developments and challenges are discussed.

PRIMARY AIMS AND MISSION OF THE ECNM

The ECNM has been developed as a multidisciplinary nonprofit collaborative initiative and network of European expert clinicians and scientists who actively collaborate and merge their efforts, with the primary aim of markedly improving recognition, diagnosis, prognostication, management, and therapy of patients with MC diseases in Europe.[57-59] Based on the complex molecular features and pathology of MC disorders and the heterogeneous clinical course and presentation of the disease, it was of utmost importance to create a multidisciplinary collaborative consortium that integrates medical specialists from various areas, including pathology, dermatology, hematology, allergy and clinical immunology, flow cytometry, and laboratory medicine within the ECNM. The experts of the ECNM are not obliged to perform specific work or to conduct certain studies in the ECNM. Rather, all work, studies, and related activities provided in the ECNM by participants are voluntary contributions.[57-59] This includes also the ECNM registry: in fact, although participation in the ECNM registry studies is highly recommended and welcome, there is no need for ECNM centers to participate. Every interested physician or researcher in Europe who works in the field of MC disorders (or plans to do so) and is affiliated with a medical center can become a member of the ECNM. However, participating centers (local groups) have to meet several requirements to qualify as a Center of Excellence or as a Reference Center in the ECNM.[57-59] A description of the ECNM and detailed information about its structure, the participating centers, and local experts, are included in the homepage of the ECNM (www.ecnm.net).[59]

TABLE I. Primary strategic goals of the ECNM

Increase awareness for MC disorders in Europe and in the United States
Support the development of networks and centers in European countries and interconnect these national networks in the ECNM
Provide all important available information about MC disorders, including most recent information, to patients and physicians
Support the development of diagnostic criteria and classifications of MC disorders, including mastocytosis and MCAS
Create and propose standards for diagnostic tests and for treatment approaches in patients with mastocytosis and/or MCAS
Support the development of diagnostic algorithms and treatment algorithms for patients with mastocytosis and/or MCAS
Develop and foster collaborations between study groups and centers in the United States (AIM centers) and Europe (ECNM centers)

Apart from numerous collaborations in the ECNM across Europe, members of the ECNM have also launched a larger number of fruitful collaborations with interested experts and centers in the United States. In addition, the ECNM has supported the development of a complementary competence network in the United States, the American Initiative in Mast Cell Diseases (AIM), which was inaugurated in 2019.[60] Furthermore, the ECNM established a scientific advisory board that includes major experts in the field (scientific advisors) from the United States.[58,59] These scientific advisory board members are invited to annual meetings of the ECNM and provide helpful advice and valuable discussion on projects and open issues.

The general aim of the ECNM is to promote awareness and to improve diagnosis, prognostication, management, and therapy in patients with MC disorders, including mastocytosis and MCAS.[58,59] To reach these general objectives, specific aims have been formulated. Major strategic goals are to provide all important available (including most recent) information about mastocytosis to patients and physicians, create and propose standards for diagnostic tests and treatment approaches, provide access to diagnostic evaluations and tests as well as specific treatments for patients in Europe, and facilitate referrals to top specialists (Table I). In order to achieve these important aims, experts and centers of the ECNM merge their activities and share their experience in regular meetings and scientific reports, which is a critical point because mastocytosis is a rare disease. The ECNM has organized a series of workshops and annual meetings as well as several working conferences in the past 20 years.[11,12,17,18,30] Another important aim is to publish new essential information resulting from ECNM projects (mainly

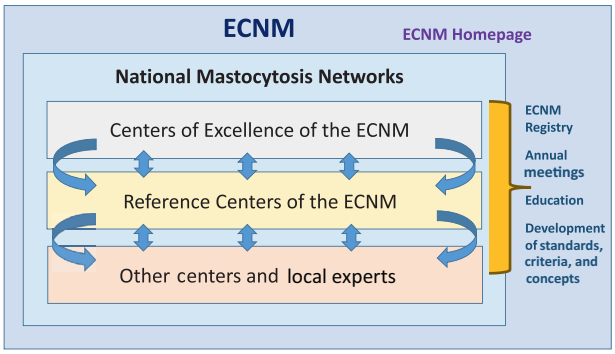

FIGURE 1. Basic structure of the ECNM. The ECNM is based on local national networks on mastocytosis where Centers of Excellence and Reference Centers are located. Whereas Centers of Excellence cover all aspects of the disease and all groups of patients, Reference Centers are only focusing on 1 specific aspect of the disease or only 1 specific group of patients. However, in this specific aspect, the Reference Centers are not only major referral sites but also serve as global referral centers based on the presence and availability of top authorities in the field. The ECNM also consists of other collaborating centers and collaborating experts who are usually staying in close collaboration with Centers of Excellence of the ECNM. All these centers and experts work together to provide the best available information and management to patients, conduct ECNM registry projects, organize annual meetings of the ECNM, provide up-to-date education, and develop standards in the diagnosis, prognostication, and therapy of MC disorders.

ECNM registry projects) in peer-reviewed journals on a regular basis.

Another major goal of the ECNM is to strengthen and expand the ECNM network activities in Europe and to foster collaboration with the United States and other countries. To reach this aim, it was of crucial importance to establish a network of Centers of Excellence and also Reference Centers for each specific topic (special aspect) in Europe (Figure 1). The network was developed in a step-wise fashion. In an initial phase (2002−2009) a limited number of Centers of Excellence (n = 19) and Reference Centers (n = 10) were inaugurated.[57] In a second phase, additional groups, centers, and countries joined.[58,59] As of 2022, a total of 45 Centers of Excellence have been established (Table II). Prior to or at the time of inauguration, new centers were visited by members of the ECNM to examine the status of the center and center type. The long-term aim is to establish at least 1 Center of Excellence in each European country, at least 2 Centers of Excellence in bigger E.U. countries, and at least 1 Reference Center for each important aspect concerning diagnosis and prognostication (pathology, dermatology, hematology, laboratory medicine, genetics) or management and therapy of patients (pediatric patients, adult patients, nonadvanced disease and advanced SM) in Europe. It is worth noting that ECNM centers sometimes change their basic structure and/or their status, depending on the availability of experts, tools, facilities, and resources. It is also noteworthy that a Center of Excellence may also qualify as a Reference Center (for a certain aspect of the disease) and, *vice versa,* a Reference Center can also expand to or develop into a Center of Excellence. In both instances, the center can maintain the status of both types of centers. Finally, it is important to state that individual experts, groups, or hospitals can also join the ECNM (usually by connecting with an established center) even if not listed as a separate Center of Excellence or Reference Center. Indeed, the ECNM actively seeks and invites interested experts, groups, and centers to join and collaborate in the ECNM.[57-59]

BASIC STRUCTURE OF THE ECNM AND DISTRIBUTION OF COMPETENCE

The ECNM is an overarching cooperative network based on local and national networks on mastocytosis in Europe, defined centers, and a community of closely collaborating physicians and scientists (Figure 1).[57-59] In the past 20 years, strong national networks dedicated to MC disorders and MC research have been developed successfully in several European countries (Table II). These national networks are an essential component of the ECNM.[58,59] The ECNM and the related local national networks consist of defined centers, local groups, and local experts. The distribution of competence and center type depends on the experience of local experts as well as local tools and facilities. There are 2 major types of centers in the ECNM, the Centers of Excellence and the Reference Centers.

Centers of Excellence

Centers of Excellence are major referral sites where experts offer vast knowledge and experience in most or all relevant aspects of the disease (all disciplines) as well as all technologies and facilities required to guarantee optimal state-of-the-art diagnosis, management, and therapy of patients with all types of MC disorders, including mastocytosis and its variants, from CM types to nonadvanced and advanced SM as well as MCAS. The Centers of Excellence are usually embedded within or connected to major university hospitals and research centers.[57,58] Centers of Excellence should include strong units and teams in the fields of dermatology, allergy, hematology, other fields in internal medicine (sometimes gastroenterology, rheumatology, osteology, neurology, or pediatrics), laboratory medicine, and pathology as well as specialized laboratories and the availability to hospitalize patients and to join in clinical trials (Table III). A major task for the team in a Center of Excellence is to provide state-of-the-art diagnostic tests and state-of-the-art therapy to all patients with MC diseases. In addition, Centers of Excellence should have facilities and units to diagnose and to treat patients with MCAS. Centers of Excellence should also establish and run local registry data sets and should use these data to join ECNM registry projects. In addition, Centers of Excellence organize meetings, including annual meetings of the ECNM. As mentioned previously, depending on experience and availability of tools, the team of a Center of Excellence can also establish and run a Reference Center in the ECNM.

Reference Centers

Reference Centers are specialized centers where experts and their teams have vast experience in a certain discipline (a certain aspect) of the disease, such as pathology, dermatology, hematology, allergy, pediatrics, or laboratory medicine. In contrast to a Center of Excellence, a Reference Center only focuses (in depth) on 1 distinct aspect of the disease. These aspects may relate to diagnostic tools and/or assays, prognostication, management, and therapy of patients with mastocytosis or the development of

TABLE II. Centers of Excellence of the ECNM: status and activities until 2022*

Center	Country	Joined	National network	Annual ECNM meeting organized in	Joined in ECNM registry projects
Aarau	Switzerland	2010	-	-	+
Aachen	Germany	2015	GCNM	-	+
Antwerp	Belgium	2017	-	2023†	+
Athens	Greece	2010	-	-	+
Basel	Switzerland	2019	SWISSCNM	2022	+
Berlin	Germany	2006	GCNM	2024†	−
Brno	Czechia	2015	-	2021	+
Budapest	Hungary	2005	-	2008	+
Bucharest	Romania	2014	-	-	+
Cologne	Germany	2003	GCNM	-	+
Freiburg	Germany	2015	GCNM	-	+
Gdansk	Poland	2004	PSM	2009	+
Graz	Austria	2010	AUCNM	-	+
Groningen	Netherlands	2003	-	2004	+
Istanbul	Turkey	2008	-	2011	+
La Louvière	Belgium	2019	-	-	+
Leipzig	Germany	2009	GCNM	-	+
Leuven	Belgium	2016	-	-	+
Linz	Austria	2011	AUCNM	-	+
Lodz	Poland	2008	PSM	-	−
London	United Kingdom	2009	-	2013, 2025†	−
Luebeck	Germany	2003	GCNM	2005	+
Luzerne	Switzerland	2018	SWISSCNM	-	+
Madrid	Spain	2002	REMA/UMHRC	-	−
Mannheim	Germany	2014	GCNM	-	+
Milano	Italy	2021	RIMA	-	+
Munich	Germany	2012	GCNM	2015	+
Naples	Italy	2005	RIMA	2006	−
Odense	Denmark	2007	-	2014	−
Oslo	Norway	2018	-	-	+
Padova	Italy	2015	RIMA	-	+
Paris	France	2002	AFIRMM	2007	−
Paris	France	2012	CEREMAST	2017	+
Pavia	Italy	2014	RIMA	-	+
Porto	Portugal	2007	-	-	−
Rotterdam	Netherlands	2019	-	-	+
Salerno	Italy	2010	RIMA	2018	+
Salzburg	Austria	2015	AUCNM	2019	−
Stanford‡	United States	2015	AIM‡		+‡
Stockholm	Sweden	2006	SMG	2010	+
Toledo	Spain	2010	REMA	-	−
Uppsala	Sweden	2015	SMG	-	+
Verona	Italy	2009	RIMA	2016	+
Vienna	Austria	2002	AUCNM	2002, 2003, 2012, 2020	+
Wroclav	Poland	2008	PSM	-	−

AFIRMM, Association Française pour les Initiatives de Recherche sur le Mastocyte et les Mastocytoses; *AUCNM,* Austrian Competence Network on Mastocytosis; *CEREMAST,* Centre National de Référence sur la Mastocytose; *GCNM,* German Competence Network on Mastocytosis; *PSM,* Polska Siec Mastocytozy (Polish Mastocytosis Network); *REMA,* Red Española de Mastocitosis; *RIMA,* Rete Italiana Mastocitosi (www.associazionerima.it); *SMG,* The Swedish Mastocytosis Group; *SWISSCNM,* Swiss Competence Network on Mastocytosis; *UMHRC,* Unidad de Mastocitosis Hospital Ramón y Cajal.

*For more details about these Centers of Excellence, the reader is referred to the ECNM homepage: www.ecnm.net.

†The Annual Meeting of the ECNM will presumably take place in Antwerp (Belgium) in 2023, in Berlin (Germany) in 2024, and in London (United Kingdom) in 2025.

‡The Stanford group is part of the AIM and joined the ECNM registry projects in a defined, special collaboration, but is not an official center of the ECNM.

certain treatment concepts.[57,58] In most instances, a major leading expert (authority) in the field coordinates and runs a Reference Center of the ECNM. Examples for a typical Reference Center are the Reference Center for hematopathology in Munich (Germany), the Reference Center for dermatology in Basel (Switzerland), or the Reference Center for flow cytometry

TABLE III. Laboratory-based and clinical aspects relevant to MC disorders

Laboratory-based aspects and features
Germline factors and germline patterns: gene variants
HαT: diagnosis and implications
Somatic *KIT* mutations: assays and interpretation of results
Somatic mutations in other genes: diagnostic assays and algorithms
Histopathological assessments, pathology, and cell morphology
Flow cytometry analysis of neoplastic MC
Serum tryptase measurements in various clinical contexts
Optimal imaging techniques (radiology) and staging
Drug development and *in vitro* drug testing
Clinical aspects
MCAS and anaphylaxis
Concomitant IgE-dependent and IgE-independent allergies
Dermatology and dermatopathology: delineating CM and SM
Hematopathology and general pathology
Gastroenterology and hepatology
Clinical hematology: management of ASM, MCL, and AHN
Neurological and psychiatric aspects in CM, SM, and MCAS
Osteology and bone pathology: osteoporosis and osteosclerosis
Perioperative management, pain and intensive care management
Pediatric aspects and management of childhood mastocytosis
Classification of CM and SM variants: application of criteria
Pharmacological aspects: drug interactions and side effects
Bacterial and viral infections in patients with CM, SM, and MCAS
SARS-CoV-2 infections in patients with CM, SM, and MCAS
Management of pregnancy in patients with CM, SM or MCAS
Development of diagnostic algorithms and classifications
Development of treatment algorithms and response criteria
Hematopoietic stem cell transplantation and immunotherapies
Preparation and conduct of clinical trials

AHN, Associated hematological neoplasm; *HαT,* hereditary alpha tryptasemia; *IgE,* immunoglobulin E; *MC,* mast cells; *SARS-CoV-2,* severe acute respiratory syndrome coronavirus 2.

in Salamanca (Spain). Reference Centers are active referral sites and are highly specialized and well trained to give information and advice in difficult cases. Depending on the site, Reference Centers can greatly support other centers in establishing the correct diagnosis, preparing a suitable management plan, or selecting the most appropriate therapy. Additional important tasks for a Reference Center of the ECNM are to develop local guidelines and recommendations and to support the development of generally accepted international standards and guidelines for the diagnosis, clinical evaluations, and management and treatment of patients with mastocytosis.[57,58] Reference Centers should also distribute updated recommendations and guidelines in their local centers, regional centers (country), and European centers (ECNM) using various communication channels, such as local and international (peer-reviewed) journals, local meetings, national network meetings, annual meetings of the ECNM, other network meetings, and other public media when appropriate. Depending on resources and experts, Reference Centers may also organize special training courses or seminars for interested students, postdocs, and physicians.

Finally, Reference Centers should also join the ECNM registry projects if possible and should conduct basic research projects, observational clinical studies, and clinical trials if possible.

TABLE IV. Researchers of the year (ROY) of the ECNM since 2014*

Name of ROY	Year of selection	Decisive discovery/contribution
Luis Escribano Mora	2014	Aberrant phenotype of neoplastic MC in SM
Lawrence B. Schwartz	2015	Tryptase as biomarker and minor criterion of SM
Hans-Peter Horny	2016	Diagnostic hematopathology evaluations in SM
Hanneke Kluin-Nelemans	2017	Cladribine as effective drug in advanced SM
Dean D. Metcalfe	2018	First consensus classification proposed
Jason Gotlib	2019	Efficacy of KIT-targeting drugs in advanced SM
Karin Hartmann	2020	Delineation of prognostic variants of MPCM
Wolfgang R. Sperr	2021	Developing prognostic score models in SM
Cem Akin	2022	Diagnostic criteria and classification of MCAS

MC, mast cells; *MCAS*, mast cell activation syndrome; *MPCM,* Maculopapular cutaneous mastocytosis; *SAB,* scientific advisory board; *SM*, systemic mastocytosis. *ROY candidates can be nominated by board members of the ECNM, by a center of the ECNM, or by another major academic center conducting research and/or patient management in the field of mastocytosis. Nominated candidates are screened for eligibility (ROY must fulfil certain criteria) and the ROY is then selected from a list of definitive candidates by voting. The voting committee consists of the board of the ECNM and the SAB of the ECNM. For more details about the ROY and the SAB, we refer the readers to the ECNM homepage: www.ecnm.net.

These studies may form a crucial basis for the development of new standards, guidelines, and diagnostic or therapeutic concepts and in developing updated versions of diagnostic, prognosis-related, and therapeutic algorithms.

Apart from Centers of Excellence and Reference Centers, other (local) centers and interested physicians or scientists without special center status, can join the ECNM and can participate in ECNM projects, usually in cooperation with a fully equipped Center of Excellence. A major goal of the ECNM is to invite and attract as many experts and physicians as possible. These partners can join as cooperating centers, cooperating scientists, and cooperating physicians. Basic science centers and their experts can join provided local experts conduct projects in the field of MC and/or mastocytosis research. In most instances, these centers and experts collaborate closely with a Reference Center or a Center of Excellence of the ECNM in the same region.

The ECNM homepage

The official homepage of the ECNM (www.ecnm.net) was prepared as a primary information tool for doctors, patients, and relatives.[57-59] The homepage contains information about the disease in general, the basic structure of the ECNM, networking activities, Centers of Excellence and Reference Centers, local experts, and the ECNM registry. Experts listed in the homepage gave their approval to be included in the homepage. The ECNM homepage is regularly updated by members of the ECNM and contains information about annual meetings, achievements of the ECNM, and the Researcher of the Year (ROY) of the

ECNM. In addition, the homepage contains links to several other (national and international) networks and patient groups as well as information about new research activities and study results published in PubMed.

DEVELOPMENT OF THE ECNM IN EUROPE SINCE 2002

The strategic aims of the ECNM are to increase awareness and recognition of MC-related disorders, provide optimal training and education to doctors and scientists, provide all available information to patients and their relatives and physicians, and improve management, diagnosis, and therapy for all patients. In addition, the ECNM provides information and advice to patient groups (self-support groups) and health authorities and assists in the development of collaborations between academic and industrial partners. Based on these goals, it has been essential to create a network of collaborating centers in the ECNM covering most regions in Europe. Overall, the long-term goal is to establish and run at least 1 or 2 Reference Centers for each discipline or key aspect of the disease in Europe and to establish and run at least 1 Center of Excellence in each European country and region. In the bigger European countries, at least 2 Centers of Excellence should be established. In several European regions and countries, these aims have been reached, and strong National Networks on Mastocytosis have been established in the past 20 years (Table II). In other European countries, the ECNM is seeking contact with interested centers and experts. Active collaborations and exchange of knowledge and experience among various centers as well as continuous education of doctors should support this development plan. The long-term goal of the ECNM is to attract and include as many interested physicians, scientists, and centers as possible. An important aspect in the development of the network is its flexibility regarding centers and regions. For example, a center with major facilities for many aspects of the disease but without access to a dermatology unit may well be recognized as a fully active Center of Excellence of the ECNM, provided that the site cooperates actively with another center (eg, a nearby hospital in the same region) where a fully equipped dermatology unit is taking care of their patients. This also applies to centers in which not all diagnostic tests or tools are available but patient-derived material can be sent to a cooperating center or even a Reference Center for diagnostic testing.

NETWORKING ACTIVITIES IN THE ECNM

Network activities include collaborations in basic science and translational research among centers, in both local areas and countries, but also across Europe and between the ECNM and other networks, such as the AIM. In addition, networking includes the organization of smaller and larger meetings dedicated to education and collaborations, such as the annual meetings of the ECNM, and the preparation of local, national, and international guidelines and recommendations in local media and peer-reviewed position papers.[57,58] Moreover, the ECNM assists the WHO and other global platforms in their efforts to develop and update diagnostic criteria and classifications in the field of mastocytosis and MCAS. The ECNM has organized annual meetings since 2002 (Table II). In addition, members of the ECNM have organized numerous smaller and larger workshops as well as several working conferences in the field of MC disorders (working conferences: 2005, 2010, 2015, 2020). In the annual meetings of the ECNM, several sessions are dedicated to strategic networking and ECNM-specific collaborations (ECNM registry projects), whereas other sessions are dedicated to new scientific results and/or education. The ECNM also supports the exchange of personnel among centers, with the aim of fostering collaborative research efforts. In the past 20 years, the ECNM conducted numerous collaborative projects in basic science, translational research, and clinical research, and published these results in peer-reviewed articles. A major emerging tool of project-specific networking within the ECNM is the ECNM registry[61] (see following paragraph).

In the past 20 years, the ECNM has established several fruitful collaborations and networking activities together with patients, their groups, and their representatives. The ECNM launched a series of patient information meetings in several European countries to support these collaborations. In addition, members of the ECNM have initiated and supported several projects in the emerging field of open innovation in science (OIS).[30,62,63] In these OIS projects, patients and their representative created a dataset and resulting recommendations to the scientific community. These recommendations, in turn, have fertilized and supported major developments in the field, both in basic science and in translational research.[17,30]

Finally, the ECNM has established a nomination award that is provided to outstanding scientists who dedicated their life and career to MC disorders. Laureates are called Researcher of the Year (ROY) and receive their award (the ECNM medal) in an annual meeting of the ECNM. Laureates (ROY) who received an ECNM medal are listed in Table IV. Their seminal discoveries and contributions to the field of mastocytosis are described in the ECNM homepage (www.ecnm.net).[59]

THE ECNM REGISTRY AND RELATED PROJECTS

Because mastocytosis is a rare disease, it was of utmost importance to collect and merge clinical and laboratory-based information from multiple centers in a harmonized way in a registry and to study the resulting data and datasets in defined multicenter registry projects. Indeed, the ECNM registry is a key tool of collaborative research on clinical aspects in patients with mastocytosis conducted within the ECNM.[61] The registry was launched in 2012.[58,59] Since then, the dataset has rapidly expanded, and by the year 2022, the total number of patients with mastocytosis included in the registry was over 5,000. The strength of the data registry of the ECNM lies in a robust data-capturing and control system as well as the fact that follow-up visits and follow-up data as well as clinical outcomes and end points are all captured. Furthermore, as novel biomarkers and concepts emerge, the marker-panels collected are regularly updated. The distribution of projects to centers is approved and the consent of each center to participate in each individual project is obtained every year at the annual meeting of the ECNM.[61] So far, a total number of 7 project waves including 35 projects have been distributed to interested centers. After distribution, the new projects are presented by the investigators in the annual meetings of the ECNM.[61] So far, a total of 10 projects have been completed and published. Several of these projects focus on prognostic markers, marker-constellation, and prognostic scores. One good example is the International Prognostic Scoring System for Mastocytosis.[26] Other projects are

TABLE V. Major discoveries and concepts arising from studies supported by the ECNM

Major discovery or concept	ECNM registry study/project	Year of publication	Reference number
Updated response criteria for patients with advanced SM	No	2022	89
Proposing updated consensus criteria for mast cell leukemia (MCL) and myelomastocytic leukemia (MML)	No	2014	42
Delineation of 2 prognostic subsets of childhood MPCM and demonstration that only the monomorphic form with small lesions persists into adulthood	No	2016	37
Clinical validation of midostaurin: first disease-modifying KIT inhibitor for patients with advanced SM/MCL	No	2016	78
Establishment of an international prognostic scoring system for patients with mastocytosis: the IPSM	Yes	2019	26
Prognostic impact of eosinophils in SM	Yes	2020	71
Establishing a prognostic score for patients with mastocytosis in the skin without bone marrow data (Fuchs score)	Yes	2021	72
Defining the clinical impact of skin lesions in patients with mastocytosis	Yes	2021	44
Prognostic role of sex and cytogenetic and molecular abnormalities in SM	Yes	2021	73
Establishing diagnostic criteria for bone marrow mastocytosis (a new WHO variant of SM since 2022)	Yes	2022	45
Proposing diagnostic criteria for mast cell activation disorders listed in the ICD-10-CM-Adjusted Code	No	2022	31
Defining clinical and molecular features of patients with various forms of MCL and delineation of prognostic MCL variants and sub-variants	Yes	2022	85
Adverse prognostic impact of organomegaly in SM	Yes	2023	86
First comprehensive user's guide in mast cell disorders: joint proposal of the ECNM and AIM	No	2022	84
Refined treatment response criteria for patients with non-advanced SM: an ECNM-AIM consortium proposal	No	2022	88
Refined treatment response criteria for patients with advanced SM/MCL: an ECNM-AIM consortium proposal	No	2022	89

ICD-10-CM, International Classification of Disease-10—Clinical Modification; *IPSM*, International Prognostic Scoring System for Mastocytosis; *MML*, myelomastocytic leukemia; *MPCM*, maculopapular cutaneous mastocytosis.

comparing treatment outcomes or certain disease features, such as bone disease, mediator-related symptoms, allergies, or other neoplasms.

BASIC SCIENCE PROJECTS, TRANSLATIONAL STUDIES, AND CLINICAL TRIALS

An essential aim of the ECNM is to support translational and clinical studies in patients with mastocytosis and other MC disorders. In addition, the ECNM consortium supports the conduct of basic science studies and preclinical projects in which clinical and translational studies are prepared or supported. One example is the preclinical studies exploring the effects of various targeted drugs and other conventional antineoplastic drugs on growth and viability of neoplastic MC.[64-69] Another example is the identification and characterization of leukemic stem cells in patients with ASM and MCL with the aim of identifying and exploiting therapeutic targets expressed in these cells.[70] This is of clinical importance because, once these targets have been identified, the use of targeted drugs may help eliminate these cells, thereby supporting the development of leukemic stem cell—eradicating and, thus, curative drug therapies in patients with advanced SM. In a separate set of studies, ECNM members focus on the development of novel drugs that block mediator production, mediator release, or mediator effects, with the aim of translating these drugs to patients with MCAS and other MC disorders.

In translational projects, members of the ECNM have validated new diagnostic markers or new prognostic variables, with the aim of improving diagnosis and/or prognostication in patients with MC disorders.[25,71-77] In addition, members of the ECNM have established prognostic scoring systems.[26-28] In other projects, members of the ECNM are testing various classes of drugs, including novel potent inhibitors of KIT D816V in clinical trials together with industrial partners. Good examples are midostaurin and avapritinib.[6,8,64,78-83] Both drugs have recently been translated into clinical practice and received approval for treatment of advanced SM by health authorities, based on preclinical studies and subsequent clinical trials.[78-83] In all these studies, members of the ECNM have participated actively. Other KIT inhibitors include imatinib and masitinib, both acting against wild-type KIT but not KIT D816V, and bezuclastinib, a novel agent suppressing KIT D816V activity.

During the past 15 years, the ECNM consortium has published a series of articles on optimal diagnosis, prognostication, management, and treatment of patients with mastocytosis and MCAS in daily practice and related diagnostic and therapeutic algorithms.[12,30,31,37,42,84-86] These publications were prepared in collaboration with their U.S. colleagues. Moreover, as mentioned previously, the ECNM consortium developed several prognostic scoring system.[26-28] Finally, members of the ECNM and of the AIM network have worked together and published a series of collaborative studies and articles providing useful treatment

TABLE VI. Major goals of the ECNM for 2023 to 2030

Attract more physicians and scientists as well as new centers and countries
Establish new scientific collaborations in the field of mastocytosis within the ECNM
Extend the number of centers and experts joining ECNM registry projects
Extend the number of ECNM registry projects and of published registry studies
Establish a solid ECNM biobank system and connect it with ECNM registry projects
Improve education and training of interested physicians and other clinical personnel
Establishing new Centers of Excellence and new Reference Centers in the ECNM
Extend and intensify existing scientific collaborations between ECNM and AIM
Foster collaborations and the support of patient groups and patient societies
Supporting OIS projects of patient groups and their representatives
Establishing a clinical study group and a related network within the ECNM
Initiating and conducting clinical trials in patients with CM and nonadvanced SM
Initiating and conducting clinical trials in patients with advanced SM
Initiating and conducting clinical trials in patients with MCAS
Evaluate the impact of genetic germ line predispositions, including HαT
Preclinical and clinical development of novel drugs and drug combinations for patients with advanced SM
Development of novel drugs for patients with CM and nonadvanced SM
Development of novel drugs for patients with MCAS and related disorders
Organization of annual meetings of the ECNM 2023 to 2030
Organization of other scientific meetings together with AIM experts
Organization of working conference on mastocytosis and MCAS in 2025 and 2030
Assist in the preparation of updated WHO criteria and WHO classification

HαT, Hereditary alpha tryptasemia.

response criteria for patients with MC disorders.[12,30,37,87-89] A compilation of the most important studies published by members of the ECNM consortium is shown in Table V. Most of these studies were performed in collaboration with members of the AIM.

AIMS OF THE ECNM FOR 2023 TO 2030

A major strategic aim for the ECNM is to further expand the network by inviting more centers and experts in the European Union to join and to work in the field of MC disorders within the ECNM. Whereas, in most of the European countries, mastocytosis is now a well-known disease, some of the European regions and countries still have no centers or local experts who are experienced in the field of MC diseases. The ECNM plans to support interested colleagues and centers in these countries and to establish new Centers of Excellence and new Reference Centers in the foreseeable future. Furthermore, the ECNM will continue to educate young interested scientists and physicians in order to maintain a high standard in the diagnosis, prognostication, and disease management. As in the past, members of the ECNM will exploit the annual meetings of the ECNM for educating and training young interested colleagues from various countries. Another goal of the ECNM is to extend interactions and collaborative projects with patient organizations in various countries. In 2010 and 2020, the ECNM organized special sessions for patients and their representatives and supported OIS projects.[63] These OIS projects were supported by members of the ECNM and AIM and used by patients to provide valuable recommendations, concerns, and other feedback to the scientific community. The final outcomes of these OIS projects were of great importance to the field. A highlighting example is the important topic of MCAS, which was discussed and developed by ECNM and AIM experts based in part on OIS projects.[29-31,62] In addition, based on these projects, MCAS criteria and a classification of MCAS were established by the scientific community. The aim of the ECNM is to further exploit collaborations with patient groups and to continue to support OIS projects in 2023 to 2030.

As mentioned, the ECNM registry will continue to provide a strong dataset platform through which new important projects will be launched on a regular basis. So far, 7 project waves, including a total of 35 projects, have been scheduled and most of these projects are ongoing or have already been published. Overall, the ECNM registry provides a major tool for conducting retrospective and prospective analyses in patients with mastocytosis. A major aim of the ECNM is to further exploit this registry in the forthcoming years. The ECNM will also focus on new important biomarkers and new treatment strategies, with the aim of improving diagnosis, prognostication, and therapy in patients with MC disorders. Members and centers of the ECNM are dedicated to further collaborate in these important projects and studies and to merge their experience, data, and activities in these studies. A summary of major goals of the ECNM for the years 2023 to 2030 is shown in Table VI.

CONCLUSIONS

In the past 20 years, since its inauguration and launch, the ECNM has made profound contributions in the field of mastocytosis and MCAS and has assisted the field by increasing recognition and awareness of MC disorders, conducting preclinical and clinical studies, supporting the field in the development and refinement of criteria and classifications, and improving diagnosis, prognostication, management, and therapy of patients with MC disorders. The ECNM is a steadily expanding network that has established numerous centers and regional (national) networks in the past 20 years. Moreover, a large number of preclinical and translational projects and studies have been launched and conducted by members of the ECNM, many of them in collaboration with their U.S. partners (ECNM-AIM cooperations) and/or with industrial collaboration partners. An emerging major tool of research within the ECNM is the ECNM registry in which over 30 projects have been launched in the past 10 years. Finally, several project clusters and studies have resulted in the development of new interventional therapies and targeted drugs. Several of these drugs have been translated into clinical application and have received approval by health authorities in the United States and Europe. In the forthcoming years, many more studies and projects will be conducted by the ECNM consortium, with the aim of acquiring new insights into the incidence, etiology, course, prognosis, and treatment outcomes

in various MC disorders. Finally, the ECNM will continue to provide a useful platform for collaborative research and translation of new important concepts and therapies.

Acknowledgments

All authors contributed equally by discussing literature material, algorithms, and ECNM-related activities and achievements. All authors contributed essentially to the ECNM by organizing annual meetings, conducting and publishing ECNM registry projects, and chairing and coordinating national competence networks and groups. Moreover, all authors listed contributed substantially by writing parts of the manuscript and all approved the final version of the document.

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REFERENCES

1. Lennert K, Parwaresch MR. Mast cells and mast cell neoplasia: a review. Histopathology 1979;3:349-65.
2. Austen KF. Systemic mastocytosis. N Engl J Med 1992;326:639-40.
3. Valent P, Akin C, Sperr WR, Horny HP, Arock M, Lechner K, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. Br J Haematol 2003; 122:1-23.
4. Valent P, Sperr WR, Schwartz LB, Horny HP. Diagnosis and classification of mast cell proliferative disorders: delineation from immunologic diseases and non-mast cell hematopoietic neoplasms. J Allergy Clin Immunol 2004;114:3-11.
5. Metcalfe DD. Mast cells and mastocytosis. Blood 2008;112:946-56.
6. Arock M, Valent P. Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. Expert Rev Hematol 2010;3: 497-516.
7. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. N Engl J Med 2015;373:163-72.
8. Reiter A, George TI, Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. Blood 2020;135:1365-76.
9. Valent P, Akin C, Sperr WR, Horny HP, Arock M, Metcalfe DD, et al. New insights into the pathogenesis of mastocytosis: emerging concepts in diagnosis and therapy. Annu Rev Pathol 2023;18:361-86.
10. Metcalfe DD. Classification and diagnosis of mastocytosis: current status. J Invest Dermatol 1991;96:2S-4S.
11. Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001;25:603-25.
12. Valent P, Akin C, Escribano L, Födinger M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007;37:435-53.
13. Valent P, Horny H-P, Li CY, Longley JB, Metcalfe DD, Parwaresch RM, et al. Mastocytosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001. p. 291-302.
14. Horny HP, Akin C, Metcalfe DD, Bain BJ, Akin C, Escribano L, et al. Mastocytosis (mast cell disease). In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. World Health Organization (WHO) Classification of Tumours. Pathology & Genetics. Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008. p. 54-63.
15. Horny HP, Akin C, Arber D, Peterson LA, Tefferi A, Metcalfe DD, et al. Mastocytosis. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 3. Lyon, France: IARC Press; 2017. p. 62-9.
16. Valent P, Akin C, Metcalfe DD. Mastocytosis:2016 updated WHO classification and novel emerging treatment concepts. Blood 2017;129:1420-7.
17. Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, et al. Updated diagnostic criteria and classification of mast cell disorders: a consensus proposal. Hemasphere 2021;5:e646.
18. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022;36:1703-19.
19. Sperr WR, Horny HP, Valent P. Spectrum of associated clonal hematologic non-mast cell lineage disorders occurring in patients with systemic mastocytosis. Int Arch Allergy Immunol 2002;127:140-2.
20. Horny HP, Sotlar K, Sperr WR, Valent P. Systemic mastocytosis with associated clonal haematological non-mast cell lineage diseases: a histopathological challenge. J Clin Pathol 2004;57:604-8.
21. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. Blood 2009;113:5727-36.
22. Pardanani A, Lim KH, Lasho TL, Finke CM, McClure RF, Li CY, et al. WHO subvariants of indolent mastocytosis: clinical details and prognostic evaluation in 159 consecutive adults. Blood 2010;115:150-1.
23. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. Allergy 2008;63:226-32.
24. Bonadonna P, Perbellini O, Passalacqua G, Caruso B, Colarossi S, Dal Fior D, et al. Clonal mast cell disorders in patients with systemic reactions to *Hymenoptera* stings and increased serum tryptase levels. J Allergy Clin Immunol 2009;123:680-6.
25. Jawhar M, Schwaab J, Hausmann D, Clemens J, Naumann N, Henzler T, et al. Splenomegaly, elevated alkaline phosphatase and mutations in the SRSF2/ASXL1/RUNX1 gene panel are strong adverse prognostic markers in patients with systemic mastocytosis. Leukemia 2016;30:2342-50.
26. Sperr WR, Kundi M, Alvarez-Twose I, van Anrooij B, Oude Elberink JNG, Gorska A, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. Lancet Haematol 2019;6:e638-49.
27. Jawhar M, Schwaab J, Álvarez-Twose I, Shoumariyeh K, Naumann N, Lübke J, et al. MARS: mutation-adjusted risk score for advanced systemic mastocytosis. J Clin Oncol 2019;37:2846-56.
28. Muñoz-González JI, Álvarez-Twose I, Jara-Acevedo M, Zanotti R, Perkins C, Jawhar M, et al. Proposed global prognostic score for systemic mastocytosis: a retrospective prognostic modelling study. Lancet Haematol 2021;8:e194-204.
29. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. J Allergy Clin Immunol 2010;126:1099-1104.e4.
30. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157:215-25.
31. Valent P, Hartmann K, Bonadonna P, Gülen T, Brockow K, Alvarez-Twose I, et al. Global classification of mast cell activation disorders: an ICD-10-CM–adjusted proposal of the ECNM-AIM consortium. J Allergy Clin Immunol Pract 2022;10:1941-50.
32. Broesby-Olsen S, Farkas DK, Vestergaard H, Hermann AP, Møller MB, Mortz CG, et al. Risk of solid cancer, cardiovascular disease, anaphylaxis, osteoporosis and fractures in patients with systemic mastocytosis: a nationwide population-based study. Am J Hematol 2016;91:1069-75.
33. Hartmann K, Henz BM. Cutaneous mastocytosis—clinical heterogeneity. Int Arch Allergy Immunol 2002;127:143-6.
34. Sokol H, Georgin-Lavialle S, Grandpeix-Guyodo C, Canioni D, Barete S, Dubreuil P, et al. Gastrointestinal involvement and manifestations in systemic mastocytosis. Inflamm Bowel Dis 2010;16:1247-53.
35. Rossini M, Zanotti R, Bonadonna P, Artuso A, Caruso B, Schena D, et al. Bone mineral density, bone turnover markers and fractures in patients with indolent systemic mastocytosis. Bone 2011;49:880-5.
36. van der Veer E, van der Goot W, de Monchy JG, Kluin-Nelemans HC, van Doormaal JJ. High prevalence of fractures and osteoporosis in patients with indolent systemic mastocytosis. Allergy 2012;67:431-8.
37. Hartmann K, Escribano L, Grattan C, Brockow K, Carter MC, Alvarez-Twose I, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol 2016;137:35-45.
38. Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. PLoS One 2008;3:e2266.
39. Moura DS, Sultan S, Georgin-Lavialle S, Barete S, Lortholary O, Gaillard R, Hermine O. Evidence for cognitive impairment in mastocytosis: prevalence, features and correlations to depression. PLoS One 2012;7:e39468.

40. Boddaert N, Salvador A, Chandesris MO, Lemaître H, Grévent D, Gauthier C, et al. Neuroimaging evidence of brain abnormalities in mastocytosis. Transl Psychiatry 2017;7:e1197.
41. Valent P, Akin C, Sperr WR, Escribano L, Arock M, Horny HP, et al. Aggressive systemic mastocytosis and related mast cell disorders: current treatment options and proposed response criteria. Leuk Res 2003;27:635-41.
42. Valent P, Sotlar K, Sperr WR, Escribano L, Yavuz S, Reiter A, et al. Refined diagnostic criteria and classification of mast cell leukemia (MCL) and myelomastocytic leukemia (MML): a consensus proposal. Ann Oncol 2014;25:1691-700.
43. Trizuljak J, Sperr WR, Nekvindová L, Elberink HO, Gleixner KV, Gorska A, et al. Clinical features and survival of patients with indolent systemic mastocytosis defined by the updated WHO classification. Allergy 2020;75:1927-38.
44. Aberer E, Sperr WR, Bretterklieber A, Avian A, Hadzijusufovic E, Kluin-Nelemans HC, et al. Clinical impact of skin lesions in mastocytosis: a multicenter study of the European Competence Network on Mastocytosis. J Invest Dermatol 2021;141:1719-27.
45. Zanotti R, Bonifacio M, Lucchini G, Sperr WR, Scaffidi L, van Anrooij B, et al. Refined diagnostic criteria for bone marrow mastocytosis: a proposal of the European Competence Network on Mastocytosis. Leukemia 2022;36:516-24.
46. Ellis JM. Urticaria pigmentosa. A report of a case with autopsy. AMA Arch Pathol 1949;48:426-9.
47. Efrati P, Klajman A, Spitz H. Mast cell leukemia? Malignant mastocytosis with leukemia-like manifestations. Blood 1957;12:869-82.
48. Friedman BI, Will JJ, Freiman DG, Braunstein H. Tissue mast cell leukemia. Blood 1958;13:70-8.
49. Schwartz LB, Sakai K, Bradford TR, Ren S, Zweiman B, Worobec AS, Metcalfe DD. The alpha form of human tryptase is the predominant type present in blood at baseline in normal subjects and is elevated in those with systemic mastocytosis. J Clin Invest 1995;96:2702-10.
50. Nagata H, Worobec AS, Oh CK, Chowdhury BA, Tannenbaum S, Suzuki Y, et al. Identification of a point mutation in the catalytic domain of the proto-oncogene c-KIT in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematologic disorder. Proc Natl Acad Sci U S A 1995;92:10560-4.
51. Longley BJ, Tyrrell L, Lu SZ, Ma YS, Langley K, Ding TG, et al. Somatic c-KIT activating mutation in urticaria pigmentosa and aggressive mastocytosis: establishment of clonality in a human mast cell neoplasm. Nat Genet 1996;12:312-4.
52. Escribano L, Orfao A, Díaz-Agustin B, Villarrubia J, Cerveró C, López A, et al. Indolent systemic mast cell disease in adults: immunophenotypic characterization of bone marrow mast cells and its diagnostic implications. Blood 1998;91:2731-6.
53. Horny HP, Sillaber C, Menke D, Kaiserling E, Wehrmann M, Stehberger B, et al. Diagnostic value of immunostaining for tryptase in patients with mastocytosis. Am J Surg Pathol 1998;22:1132-40.
54. Sperr WR, Escribano L, Jordan JH, Schernthaner GH, Kundi M, Horny HP, et al. Morphologic properties of neoplastic mast cells: delineation of stages of maturation and implication for cytological grading of mastocytosis. Leuk Res 2001;25:529-36.
55. Fritsche-Polanz R, Jordan JH, Feix A, Sperr WR, Sunder-Plassmann G, Valent P, et al. Mutation analysis of C-KIT in patients with myelodysplastic syndromes without mastocytosis and cases of systemic mastocytosis. Br J Haematol 2001;113:357-64.
56. Valent P, Escribano L, Parwaresch RM, Schemmel V, Schwartz LB, Sotlar K, et al. Recent advances in mastocytosis research: summary of the Vienna Mastocytosis Meeting 1998. Int Arch Allergy Immunol 1999;120:1-7.
57. Valent P, Arock M, Bischoff SC, Bühring HJ, Brockow K, Escribano L, et al. The European Competence Network on Mastocytosis (ECNM). Wien Klin Wochenschr 2004;116:647-51.
58. Valent P, Arock M, Bonadonna P, Brockow K, Broesby-Olsen S, Escribano L, et al. European Competence Network on Mastocytosis (ECNM): 10-year jubilee, update, and future perspectives. Wien Klin Wochenschr 2012;124:807-14.
59. The European Competence Network on Mastocytosis—ECNM. Accessed March 11, 2023. https://ecnm.meduniwien.ac.at/
60. Gotlib J, George TI, Carter MC, Austen KF, Bochner B, Dwyer DF, et al. Proceedings from the Inaugural American Initiative in Mast Cell Diseases (AIM) Investigator Conference. J Allergy Clin Immunol 2021;147:2043-52.
61. Valent P, Oude Elberink JNG, Gorska A, Lange M, Zanotti R, van Anrooij B, et al. The data registry of the European Competence Network on Mastocytosis (ECNM): set up, projects, and perspectives. J Allergy Clin Immunol Pract 2019;7:81-7.
62. Jennings S, Russell N, Jennings B, Slee V, Sterling L, Castells M, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. J Allergy Clin Immunol Pract 2014;2:70-6.
63. Jennings SV, Finnerty CC, Hobart JS, Martín-Martínez M, Sinclair KA, Slee VM, et al. Mast cell diseases in practice and research: issues and perspectives raised by patients and their recommendations to the scientific community and beyond. J Allergy Clin Immunol Pract 2022;10:2039-51.
64. Gotlib J, Berubé C, Growney JD, Chen CC, George TI, Williams C, et al. Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V KIT mutation. Blood 2005;106:2865-70.
65. Gleixner KV, Mayerhofer M, Aichberger KJ, Derdak S, Sonneck K, Böhm A, et al. PKC412 inhibits in vitro growth of neoplastic human mast cells expressing the D816V-mutated variant of KIT: comparison with AMN107, imatinib, and cladribine (2CdA) and evaluation of cooperative drug effects. Blood 2006;107:752-9.
66. Gleixner KV, Mayerhofer M, Sonneck K, Gruze A, Samorapoompichit P, Baumgartner C, et al. Synergistic growth-inhibitory effects of two tyrosine kinase inhibitors, dasatinib and PKC412, on neoplastic mast cells expressing the D816V-mutated oncogenic variant of KIT. Haematologica 2007;92:1451-9.
67. Krauth MT, Mirkina I, Herrmann H, Baumgartner C, Kneidinger M, Valent P. Midostaurin (PKC412) inhibits immunoglobulin E−dependent activation and mediator release in human blood basophils and mast cells. Clin Exp Allergy 2009;39:1711-20.
68. Lübke J, Naumann N, Kluger S, Schwaab J, Metzgeroth G, Evans E, et al. Inhibitory effects of midostaurin and avapritinib on myeloid progenitors derived from patients with KIT D816V positive advanced systemic mastocytosis. Leukemia 2019;33:1195-205.
69. Degenfeld-Schonburg L, Gamperl S, Stefanzl G, Schruef AK, Sadovnik I, Bauer K, et al. Antineoplastic efficacy profiles of avapritinib and nintedanib in KIT D816V+ systemic mastocytosis: a preclinical study. Am J Cancer Res 2023;13:355-78.
70. Eisenwort G, Sadovnik I, Schwaab J, Jawhar M, Keller A, Stefanzl G, et al. Identification of a leukemia-initiating stem cell in human mast cell leukemia. Leukemia 2019;33:2673-84.
71. Kluin-Nelemans HC, Reiter A, Illerhaus A, van Anrooij B, Hartmann K, Span LFR, et al. Prognostic impact of eosinophils in mastocytosis: analysis of 2350 patients collected in the ECNM Registry. Leukemia 2020;34:1090-101.
72. Fuchs D, Kilbertus A, Kofler K, von Bubnoff N, Shoumariyeh K, Zanotti R, et al. Scoring the risk of having systemic mastocytosis in adult patients with mastocytosis in the skin. J Allergy Clin Immunol Pract 2021;9:1705-1712.e4.
73. Kluin-Nelemans HC, Jawhar M, Reiter A, van Anrooij B, Gotlib J, Hartmann K, et al. Cytogenetic and molecular aberrations and worse outcome for male patients in systemic mastocytosis. Theranostics 2021;11:292-303.
74. Gebhard J, Horny HP, Kristensen T, Broesby-Olsen S, Zink A, Biedermann T, et al. Validation of dermatopathological criteria to diagnose cutaneous lesions of mastocytosis: importance of KIT D816V mutation analysis. J Eur Acad Dermatol Venereol 2022;36:1367-75.
75. Navarro-Navarro P, Alvarez-Twose I, Pérez-Pons A, Henriques A, Mayado A, García-Montero AC, et al. KITD816V mutation in blood for the diagnostic screening of systemic mastocytosis and mast cell activation syndromes KITD816V in blood of mastocytosis and MCAS. Allergy. 2023;78:1347-59.
76. Alvarez-Twose I, González de Olano D, Sánchez-Muñoz L, Matito A, Esteban-López MI, Vega A, et al. Clinical, biological and molecular characteristics of clonal mast cell disorders presenting with systemic mast cell activation symptoms. J Allergy Clin Immunol 2010;125:1269-78.
77. Hartmann K, Wagner N, Rabenhorst A, Pflanz L, Leja S, Förster A, et al. Serum IL-31 levels are increased in a subset of patients with mastocytosis and correlate with disease severity in adult patients. J Allergy Clin Immunol 2013;132:232-5.
78. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-41.
79. Hartmann K, Gotlib J, Akin C, Hermine O, Awan FT, Hexner E, et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. J Allergy Clin Immunol 2020;146:356-366.e4.
80. Gotlib J, Reiter A, Radia DH, Deininger MW, George TI, Panse J, et al. Efficacy and safety of avapritinib in advanced systemic mastocytosis: interim analysis of the phase 2 PATHFINDER trial. Nat Med 2021;27:2192-9.
81. DeAngelo DJ, Radia DH, George TI, Robinson WA, Quiery AT, Drummond MW, et al. Safety and efficacy of avapritinib in advanced systemic mastocytosis: the phase 1 EXPLORER trial. Nat Med 2021;27:2183-91.
82. Reiter A, Gotlib J, Álvarez-Twose I, Radia DH, Lübke J, Bobbili PJ, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. Leukemia 2022;36:2108-20.
83. Gotlib J, Reiter A, DeAngelo DJ. Avapritinib for advanced systemic mastocytosis. Blood 2022;140:1667-73.

84. Valent P, Hartmann K, Schwaab J, Alvarez-Twose I, Brockow K, Bonadonna P, et al. Personalized management strategies in mast cell disorders: ECNM-AIM user's guide for daily clinical practice. J Allergy Clin Immunol Pract 2022; 10:1999-2012.e6.
85. Kennedy VE, Perkins C, Reiter A, Jawhar M, Lübke J, Kluin-Nelemans HC, et al. Mast cell leukemia: clinical and molecular features and survival outcomes of patients in the ECNM Registry. Blood Adv 2023;7:1713-24.
86. Lübke J, Schwaab J, Christen D, Elberink HO, Span B, Niedoszytko M, et al. Prognostic impact of organomegaly in mastocytosis: an analysis of the European Competence Network on Mastocytosis. J Allergy Clin Immunol Pract 2023;11:581-590.e5.
87. Gotlib J, Pardanani A, Akin C, Reiter A, George T, Hermine O, et al. International Working Group—Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) & European Competence Network on Mastocytosis (ECNM) consensus response criteria in advanced systemic mastocytosis. Blood 2013;121:2393-401.
88. Pyatilova P, Akin C, Alvarez-Twose I, Arock M, Bonadonna P, Brockow K, et al. Refined treatment response criteria for indolent systemic mastocytosis proposed by the ECNM-AIM consortium. J Allergy Clin Immunol Pract 2022;10:2015-24.
89. Gotlib J, Schwaab J, Shomali W, George TI, Radia DH, Castells M, et al. Proposed European Competence Network on Mastocytosis—American Initiative in Mast Cell Diseases (ECNM-AIM) response criteria in advanced systemic mastocytosis. J Allergy Clin Immunol Pract 2022;10:2025-20238.e1.