Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-079 Avapritinib

Stand: Mai 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Avapritinib
[zur Behandlung der fortgeschrittenen systemischen Mastozytose]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use); Teil A: • IV. Dinatriumcromoglycat (DNCG)-haltige Arzneimittel (oral) bei systemischer Mastozytose Anlage I zum Abschnitt F der Arzneimittel-Richtlinie Gesetzliche Verordnungsausschlüsse in Arzneimittelversorgung und zugelassene Ausnahmen; Zugelassene Ausnahmen zum gesetzlichen Verordnungsausschluss nach § 34 Abs. 1 Satz 2 SGB V (OTC-Übersicht): • 15. Dinatriumcromoglycat (DNCG)-haltige Arzneimittel (oral) nur zur symptomatischen Behandlung der systemischen Mastozytose Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Midostaurin: Beschluss vom 02.05.2024
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Avapritinib L01EX18 AYVAKYT	<u>Zugelassenes Anwendungsgebiet:</u> AYVAKYT ist als Monotherapie zur Behandlung erwachsener Patienten mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL) nach zumindest einer systemischen Therapie indiziert.
Midostaurin L01EX10 Rydapt	Rydapt wird angewendet als Monotherapie zur Behandlung erwachsener Patienten mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-079 Avapritinib

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. April 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AdvSM-SAF	Advanced Systemic Mastocytosis Symptom Assessment Form
ASM	Aggressive systemic mastocytosis
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ECNM	European Competence Network on Mastocytosis
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCT	Hematopoietic stem cell transplantation
HR	Hazard Ratio
ICB	intracranial bleeding
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISM	Indolent systemic mastocytosis
ISM	indolente SM
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
KI	Konfidenzintervall
LoE	Level of Evidence
MCL	Mast cell leukemia
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SM	Systemic mastocytosis
SM-AHN	Systemic mastocytosis with an associated hematologic neoplasm
SSM	Smoldering systemic mastocytosis
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung erwachsener Personen mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL).

Hinweis zur Synopse: „Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt“.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Mastozytose durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 02.04.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 89 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurde insgesamt 1 Referenz eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenz.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine systematischen Reviews identifiziert.

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), 2025 [1].

Systemic Mastocytosis, Version 1.2025

Zielsetzung/Fragestellung

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Systemic Mastocytosis provide recommendations for the diagnosis and comprehensive care of patients with SM. Management of CM is not included in these guidelines.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz zu Empfehlungen für die indolente systemische Mastozytose (ISM) mit mittelschweren bis schweren Symptomen, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu,
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft teilweise zu (vgl. *Recherche/Suchzeitraum*)
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft teilweise zu (Referenzen nicht immer eindeutig den Empfehlungen bzw. nur über Hintergrundtext zuzuordnen);
- Regelmäßige Überprüfung der Aktualität gesichert: trifft nicht zu.

Recherche/Suchzeitraum:

- an electronic search of the PubMed database was performed to obtain key literature in Systemic Mastocytosis published since the previous Guidelines update using the following search term: systemic mastocytosis. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.
- Suchzeitraum und kritische Bewertung: Keine Informationen

LoE/GoR:

- NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

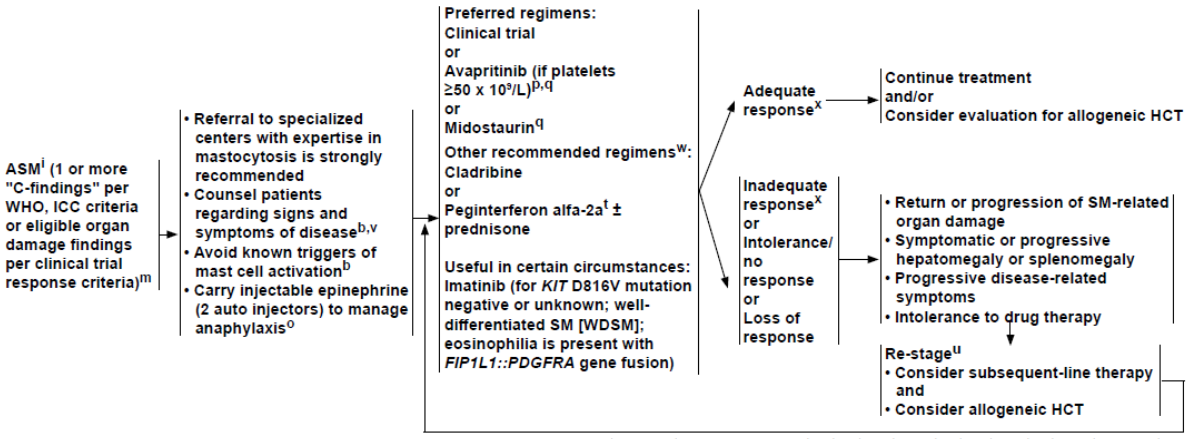
All recommendations are considered appropriate.

Sonstige methodische Hinweise

- Der Diskussionsteil der NCCN-Leitlinie befindet sich in einem Aktualisierungsprozess. Die letzte Diskussions-Version ist vom 24.04.2024.

Empfehlungen

TREATMENT FOR AGGRESSIVE SYSTEMIC MASTOCYTOSIS[l]



[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (SM-J). Multidisciplinary collaboration with subspecialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (SM-L).

[i] Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-D).

[l] Adverse Prognostic Variables and Risk stratification in Systemic Mastocytosis (SM-I).

[m] IWG-MRT-ECNM and modified IWG-MRT-ECNM criteria are used to establish eligible organ damage findings for clinical trial enrollment and to adjudicate response to therapy. The proposed ECNM-AIM response criteria use the same organ damage to assess response (SM-G). B- and C-findings are used for the diagnosis of the WHO subtype of SM (SM-D, SM-E, SM-F).

[o] See SM-K for anti-mediator drug therapy approaches for mast cell activation symptoms.

[p] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10⁹/L.

[q] Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.

[t] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.

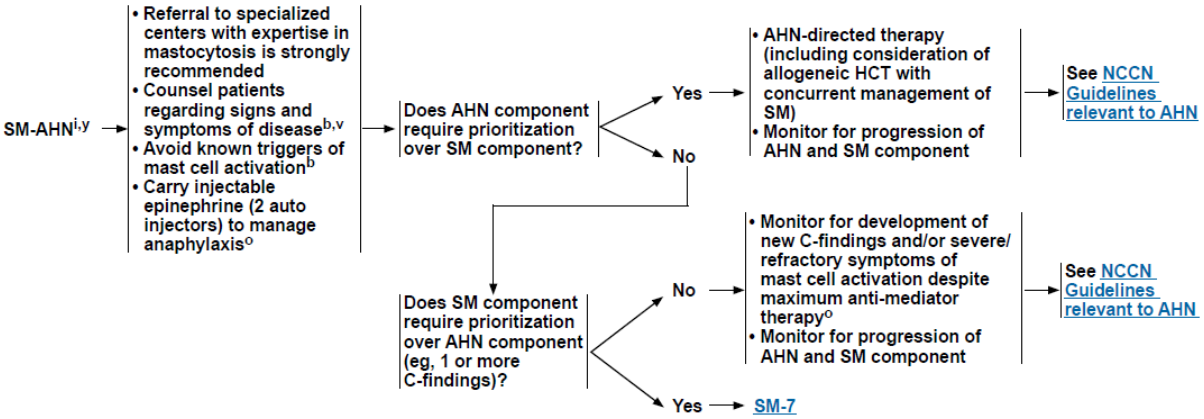
[u] Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.

[v] Taylor F, et al. Leuk Res 2021;108:106606.

[w] For patients with advanced SM, cladribine may be useful when rapid debulking of disease is required whereas peginterferon alfa-2a, which has a cytostatic mechanism of action, may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction.

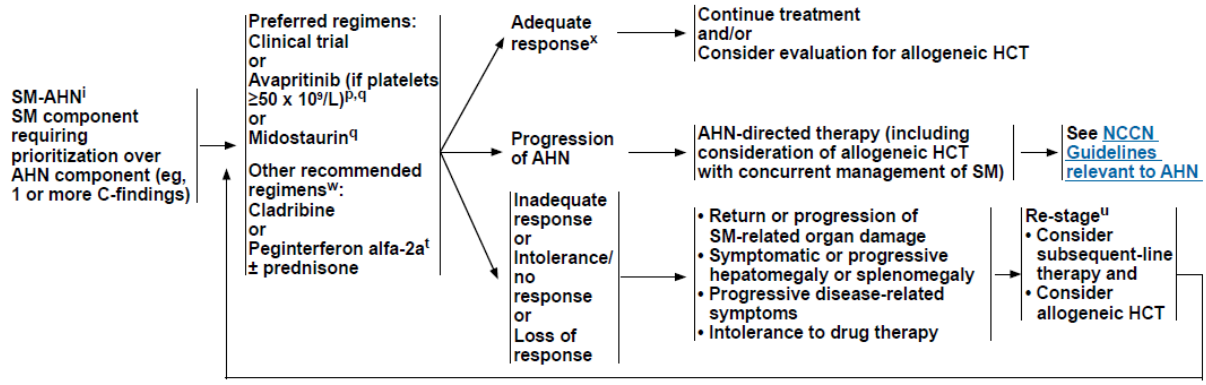
[x] See organ damage assessment and response criteria (SM-G). Clinical benefit may not reach the threshold of the clinical trial response criteria.

TREATMENT FOR SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM[l]



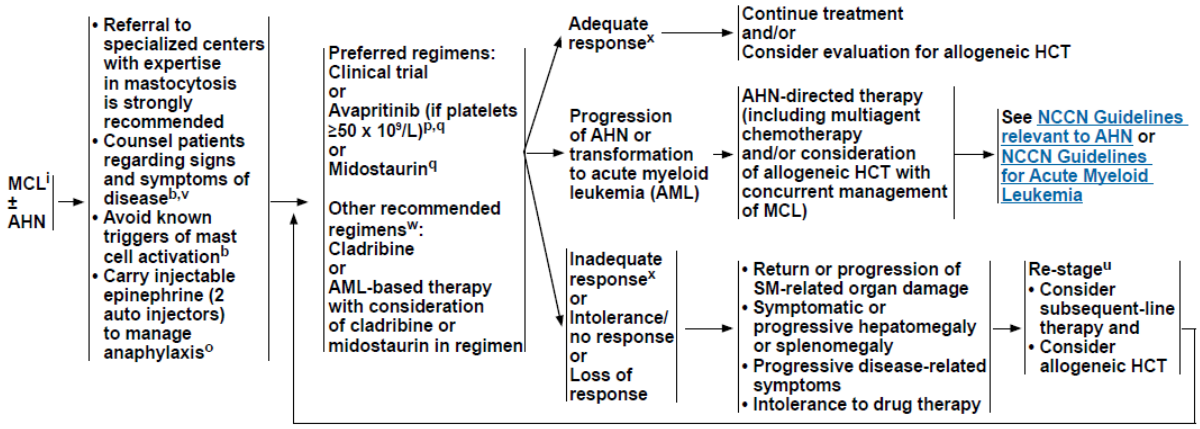
[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (SM-J). Multidisciplinary collaboration with subspecialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (SM-L).
[i] Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-D).
[l] Adverse Prognostic Variables and Risk stratification in Systemic Mastocytosis (SM-I).
[o] See SM-K for anti-mediator drug therapy approaches for mast cell activation symptoms.
[v] Taylor F, et al. Leuk Res 2021;108:106606.
[y] These algorithms refer to SM-AHN with myeloid neoplasms, which comprise the majority of cases.

TREATMENT FOR SYSTEMIC MASTOCYTOSIS WITH AN ASSOCIATED HEMATOLOGIC NEOPLASM[l]



[i] Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-D).
[l] Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-I).
[p] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10⁹/L.
[q] Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[t] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.
[u] Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.
[w] For patients with advanced SM, cladribine may be useful when rapid debulking of disease is required whereas peginterferon alfa-2a, which has a cytostatic mechanism of action, may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction.
[x] See organ damage assessment and response criteria (SM-G). Clinical benefit may not reach the threshold of the clinical trial response criteria.

TREATMENT FOR MAST CELL LEUKEMIA ± ASSOCIATED HEMATOLOGIC NEOPLASM[l,z]



[b] Patients should be counseled about the signs/symptoms and potential triggers of mast cell activation (SM-J). Multidisciplinary collaboration with subspecialists (eg, anesthesia for procedures/surgery; high-risk obstetrics for pregnancy) is recommended (SM-L).
[i] Diagnostic Criteria for the Variants of Systemic Mastocytosis (SM-D).
[l] Adverse Prognostic Variables and Risk Stratification in Systemic Mastocytosis (SM-I).
[o] See SM-K for anti-mediator drug therapy approaches for mast cell activation symptoms.
[p] Avapritinib is not recommended for the treatment of patients with platelet counts of less than 50 X 10⁹/L.
[q] Refer to the package insert for the full prescribing information, dose modifications, and monitoring for adverse reactions: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[u] Bone marrow aspirate and biopsy, serum tryptase level, and additional staging studies should be performed as clinically indicated (if supported by increased symptoms and signs of progression). See Discussion.
[v] Taylor F, et al. Leuk Res 2021;108:106606.
[x] See organ damage assessment and response criteria (SM-G). Clinical benefit may not reach the threshold of the clinical trial response criteria.
[z] Patients with chronic MCL have no organ damage. However, treatment should be considered given the poor prognosis of MCL.

Treatment Recommendations

Potential cytoreductive options for advanced SM include avapritinib, midostaurin, cladribine, or peginterferon alfa-2a. Peginterferon alfa-2a is an option for ASM and SM-AHN (when the SM component requires prioritization over the AHN component) but is not recommended for MCL with or without an AHN. In patients with SM-AHN, an initial assessment is undertaken to determine whether the SM component or the AHN component requires prioritization.

Cytoreductive Therapy

Enrollment in a clinical trial, avapritinib (if platelet counts are ≥50 x 109/L),39,40 and midostaurin38,176,177 are preferred regimens and cladribine169-171 and peginterferon alfa-2a (± prednisone)172-175 are other recommended regimens for patients with ASM, SM-AHN (when the SM component requires prioritization over the AHN component), and MCL (with or without an AHN) (except for peginterferon alfa-2a ± prednisone). Imatinib is included as a useful in certain circumstances treatment option for the rare patients with ASM (for KIT D816V mutation negative after testing with a high-sensitivity assay or unknown, WDSM, or if eosinophilia is present with FIP1L1::PDGFRA gene fusion, which operationally redefines the patients as having a myeloid/lymphoid neoplasm with eosinophilia and tyrosine kinase gene fusions as defined by the WHO and ICC).21,178-184

- Avapritinib

Avapritinib, a potent and selective inhibitor of KIT D816V, has demonstrated activity in patients with ISM and advanced SM40,168 and is FDA-approved for the treatment of adult patients with ISM and advanced SM, including ASM, SM-AHN, and MCL.

Advanced SM

Data from the phase I EXPLORER trial, which consisted of 53 evaluable patients with advanced SM (ASM, n = 3; SM-AHN, n = 37; MCL, n = 13) treated with a dose of 30 to 400 mg once daily (dose escalation and expansion stages), revealed an overall response rate (ORR) of 75% (95% CI, 62%–86%) (100% [95% CI, 29%–100%] for ASM, 76% [95% CI, 59%– 88%] for SM-AHN, and 69% [95% CI, 39%–91%] for MCL), per the mIWGMRT- ECNM response criteria.39 Ninety-two percent, 80%, and 99% of patients reported a 50% or greater decrease from baseline in bone marrow mast cells, KIT D816V variant allele fraction, and serum tryptase, respectively. A decrease of 35% or greater in spleen volume from baseline was obtained in 82% of patients. Across all patients (n = 86), the most common grade 3 and above non-hematologic adverse events were fatigue (9%) and vomiting (5%) while the most common grade 3 and above nonhematologic adverse events were thrombocytopenia (34%), anemia (30%), and neutropenia (15%). There were nine cases of intracranial bleeding (ICB) in patients with advanced SM (13% of 69 patients in the advanced SM safety population), seven of which were associated with antecedent severe thrombocytopenia.

A pre-specified interim analysis of the phase II PATHFINDER trial, which comprised 32 evaluable patients with advanced SM (ASM, n = 2; SMAHN, n = 26; MCL, n = 4) treated with avapritinib at a starting dose of 200 mg once daily, reported an ORR of 75% (95% CI, 57%–89%), as assessed by the mIWG-MRT-ECNM response criteria.40 The ORR was 100% (95% CI, 16%–100%), 81% (95% CI, 61%–93%), and 25% (1%– 81%) in patients with ASM, SM-AHN, and MCL, respectively. The safety population (n = 62) was used to assess secondary endpoints. Patients experienced reductions in objective measures of mast cell disease burden. The percentages of patients who achieved a 50% or greater decrease from baseline in bone marrow mast cells, KIT D816V variant allele fraction, and serum tryptase were 88%, 60%, and 93%, respectively. A decrease of 35% or greater in spleen volume from baseline was obtained in 66% of patients. An amelioration in patient-reported symptoms, as assessed by the AdvSM-SAF total symptom score, was also reported (P < .001). The most common grade 3 or above hematologic adverse events were neutropenia, thrombocytopenia, and anemia, and occurred in 24%, 16%, and 16% of patients, respectively. The most common grade 3 or above nonhematologic adverse events were increased blood ALP (5%), peripheral edema (3%), periorbital edema (3%), and fatigue (3%). The study reported one instance (1.6%) of ICB in a patient with severe thrombocytopenia at baseline. As patients with severe thrombocytopenia at baseline had an increased risk of ICB, the study protocols for both the EXPLORER and PATHFINDER trials were amended to exclude patients with platelet counts <50 x 109/L as part of the mitigation strategies to reduce ICB.39,40

Comparison between avapritinib and best available therapy was performed in one retrospective study that pooled data from a multi-center study whereby patients with advanced SM were treated with best available therapy and data from the EXPLORER and PATHFINDER trials.185 Median OS was significantly improved in patients treated with avapritinib (49.0 months [95% CI, 46.9 months–not estimable] vs. 26.8 months [95% CI, 18.2–39.7 months]; adjusted hazard ratio [HR], 0.48; 95% CI, 0.29– 0.79; P = .004). Data further demonstrated that avapritinib treatment was associated with improved OS compared to midostaurin (HR, 0.59; 95% CI, 0.36–0.97; P < .001) and cladribine (HR, 0.32; 95% CI, 0.15–0.67; P = .003).186 OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy.187 The duration of treatment (HR, 0.36; 95% CI, 0.26–0.51; P < .001) and the maximum decrease in serum tryptase level (mean difference of -60.3%; 95% CI, -72.8% to -47.9%; P < .001) were significantly higher in patients with advanced SM treated with avapritinib.185 The efficacy of avapritinib in patients with advanced SM was established irrespective of prior therapies or S/A/R mutation status.188

- Midostaurin

Midostaurin, an oral multikinase inhibitor with activity against D816Vmutated KIT, has demonstrated activity for the treatment of advanced SM38,176,177 and is FDA-approved only for patients with a diagnosis of ASM, SM-AHN, or MCL, although it has also been shown to be effective for patients with ISM and severe symptoms related to mast cell mediator release or skin infiltration in a small phase II clinical trial.189

In an open-label study of 116 patients with advanced SM, 89 patients had evaluable mastocytosis-related organ damage: 16 patients with ASM, 57 patients with SM-AHN, and 16 patients with MCL. Using modified Valent and Cheson response criteria, treatment with midostaurin (100 mg twice daily) resulted in an ORR of 60% (45% of the patients had a major response, defined as complete resolution of at least one type of mastocytosis-related organ damage).38 Response rates were similar across all subtypes of advanced SM, KIT mutation status (63% for patients who were KIT D816V mutation-positive and 44% for those who were KIT D816V mutation-negative or had unknown mutation status), or exposure to previous therapy. The median OS and PFS were 29 months and 14 months, respectively. The median OS and PFS were longer for patients with ASM (not reached and 29 months, respectively) than for patients with SM-AHN (21 months and 11 months, respectively) and MCL (9 months and 11 months, respectively). In a multivariate analysis, a subtype of advanced SM other than MCL and greater than or equal to 50% reduction of bone marrow mast cell burden were identified as independent predictors of longer OS. Low-grade nausea, vomiting, and diarrhea were the most frequent adverse events. New or worsening grade 3 or 4 neutropenia, anemia, and thrombocytopenia occurred in 24%, 41%, and 29% of patients, respectively, and were more common in patients with pre-existing cytopenias.

A study that evaluated the impact of KIT D816V mutation and other molecular markers on the clinical outcome of 38 patients with advanced SM treated with midostaurin found that the ORR, median duration of midostaurin treatment, and OS were significantly higher in patients with an S/A/Rneg (vs. S/A/Rpos) mutation profile and in patients with a greater than or equal to 25% (vs. <25%) reduction in the RNA expressed allele burden.190 The acquisition of additional mutations in KRAS, NRAS, RUNX1, IDH2, or NPM1 genes was identified in patients with disease progression. Another study reported an amelioration in the mast cell mediator-related symptoms in patients with advanced SM who were treated with midostaurin.191

- Cladribine

Cladribine (2-chlorodeoxyadenosine) is not approved by the FDA for SM, but is used on an off-label basis because of its activity across all subtypes of SM, including MCL refractory to prior cytoreductive therapy.169-

171 Cladribine may be particularly useful for patients with advanced SM when rapid debulking of disease is required.

In an analysis, treatment with cladribine resulted in an ORR of 56%, 50%, and 55%, in patients with ISM, ASM, and SM-AHN, respectively.170 The presence of circulating immature myeloid cells was a predictor of inferior response. In a study that reported the long-term safety and efficacy of cladribine in 68 patients with SM, the ORR was 72%, split between 92% for patients with ISM (major/partial 56%/36%) and 50% for those with advanced SM (major/partial 38%/13%).171 The median duration of response was 4 years and 3 years for ISM and ASM, respectively. In a multivariate analysis, only mastocytosis subtypes (SM-AHN vs. ISM; P = .02 and ASM vs. ISM; P = .006) and age >50 years at diagnosis were independently associated with mortality. Lymphopenia (82%), neutropenia (47%), and opportunistic infections (13%) were the most frequent grade 3 or 4 toxicities.

- Peginterferon alfa-2a with or without prednisone

Interferon alfa (with or without prednisone) carries the potential to induce a marked reduction in serum and urine metabolites of mast cell activation, reduce symptoms related to mast cell mediator release, resolve cutaneous lesions, improve skeletal disease, and improve both bone marrow mast cell burden and C-findings, across all subtypes of SM.172-175 However, because of their cytostatic mechanism of action, responses may take longer to emerge, and the use of interferons may be more suitable for patients with slowly progressive disease (PD) without the need for rapid cytoreduction. In the current era of KIT inhibitors, the therapeutic value of interferon therapy is less clear.

- Imatinib

Imatinib is FDA-approved for the treatment of adult patients with ASM without the KIT D816V mutation or with unknown KIT mutational status and is very effective in the treatment of patients with eosinophilia-associated myeloid neoplasms characterized by the FIP1L1::PDGFRA gene fusion.93,94 It has also shown activity against the KIT F522C transmembrane mutation, V560G juxtamembrane mutation, germline K509I mutation, deletion of codon 419 in exon 8, and p.A502_Y503dup mutation in exon 9.21,178-184 In a study that evaluated the efficacy of imatinib in 10 patients with SM lacking the KIT D816V mutation and meeting criteria for WDSM (including 3 patients with ISM and 3 patients with MCL), imatinib resulted in an ORR of 50%, including early and sustained complete response (CR) in four patients and partial response (PR) in one patient with wild-type KIT.21

21. Alvarez-Twose I, Matito A, Morgado JM, et al. Imatinib in systemic mastocytosis: a phase IV clinical trial in patients lacking exon 17 KIT mutations and review of the literature. Oncotarget 2017;8:68950-68963.

38. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-2541.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 04 of 12, April 2025) am 01.04.2025

#	Suchschritt
1	[mh "Mast Cell Activation Disorders"]
2	(mastocytos* OR (("mast cell activation") NEXT (syndrome* OR disease* OR disorder*)) OR ("mast cell" NEXT (syndrome* OR disease* OR disorder*))):ti,ab,kw
3	(mastocytoma* OR (("mast cell" OR mastcell) NEXT (leukemia* OR leukaemia* OR leucemia* OR leucaemia* OR tumour* OR tumor* OR neoplas* OR sarcoma*))):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Apr 2020 to present, in Cochrane Reviews

Leitlinien und systematische Reviews in PubMed am 01.04.2025

verwendete Suchfilter für Leitlinien:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendete Suchfilter für systematische Reviews:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	Mast Cell Activation Disorders[mh]
2	mastocytos*[tiab] OR ("mast cell activation"[tiab] AND (syndrome*[tiab] OR disease*[tiab] OR disorder*[tiab])) OR "mast cell syndrome*"[tiab] OR "mast cell disease*"[tiab] OR "mast cell disorder*"[tiab]
3	mastocytoma*[tiab] OR (("mast cell"[tiab] OR mastcell[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab] OR tumour*[tiab] OR tumor[tiab] OR tumors[tiab] OR neoplas*[tiab] OR sarcoma*[tiab]))
4	#1 OR #2 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(#5) AND ("2020/04/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
8	(#4) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella

#	Suchschritt
	review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
9	(#8) AND ("2020/04/01"[PDAT] : "3000"[PDAT])
10	(#9) NOT "The Cochrane database of systematic reviews"[Journal]
11	(#10) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
12	(#11) NOT (#7)

Iterative Handsuche nach grauer Literatur, abgeschlossen am 02.04.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2025-B-079

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Sachverständige	
Datum	23. Mai 2025

Indikation
Behandlung erwachsener Patienten mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL) nach zumindest einer systemischen Therapie.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Die Systemische Mastozytose (SM) ist eine seltene hämatologische Stammzellerkrankung. In der Erstlinientherapie der Behandlung erwachsener Patientinnen und Patienten (Pat.) mit aggressiver systemischer Mastozytose (ASM), systemischer Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) oder Mastzellleukämie (MCL) nach zumindest einer systemischen Therapie.AdvSM ist nur der Multikinase-/KIT-Inhibitor Midostaurin zugelassen. Standard in der Zweitlinientherapie ist

- Avapritinib
- Midostaurin bei Pat., die in der Erstlinientherapie nicht mit Midostaurin behandelt wurden.

Stand des Wissens

Die Systemische Mastozytose (SM) ist eine seltene hämatologische Stammzellerkrankung [1]. Die WHO-Klassifikation 2022 unterscheidet die Subtypen indolente systemische Mastozytose (ISM), ‚Smoldering SM' (SSM), die neu definierte ‚Bone Marrow Mastocytosis' (BMM), aggressive systemische Mastozytose (ASM), systemische Mastozytose mit assoziierter hämatologischer Neoplasie (SM-AHN) und die Mastzellleukämie (MCL) [2]. In der Literatur werden angesichts von Klinik und Verlauf ISM, BMM und SSM als non-AdvSM zusammengefasst und ASM, SM-AHN und MCL als AdvSM [3].

Ihre genetische Grundlage ist die *KIT* D816V Mutation, die sich bei >90% der Pat. findet. Pat. mit AdvSM leiden unter einer Vielzahl von belastenden Symptomen, überwiegend verursacht durch Organdysfunktion als direkte Folge der Infiltration von Mastzellen und Zellen anderer, im Krankheitsprozess beteiligter Zellreihen (z.B. Monozyten, Eosinophile). Betroffen sind vor allem Knochenmark, Leber, Milz und Gastrointestinaltrakt. Des Weiteren kommt es durch die Freisetzung von Mastzellmediatoren u. a. zu allergischen Reaktionen, Flushs. Unverträglichkeiten und/oder

Diarrhöen. Die Erkrankung ist regelmäßig von einem mitunter ausgeprägten chronischen Müdigkeitssyndrom (Fatigue) begleitet. Durch verbesserte Diagnostik, durch erhöhte Aufmerksamkeit versorgender Ärzte (z.B. häufigere Tryptase-Bestimmung, Nachweis der *KIT* D816V Mutation z.B. im Rahmen von NGS-Diagnostik) ist in den letzten Jahren eine zunehmende Zahl an Pat. mit AdvSM in Deutschland diagnostiziert worden.

In der Erstlinientherapie der AdvSM ist nur der Multikinase-/KIT-Inhibitor Midostaurin zugelassen [4].

Seit März 2022 ist Avapritinib für Pat. nach mindestens einer systemischen Vortherapie zugelassen. Bei Avapritinib handelt es sich um einen spezifischen KIT-Inhibitor, die Zulassung erfolgte auf Basis zweier nicht-randomisierter Studien EXPLORER (Phase I) und PATHFINDER (Phase II) [5-8]. Die empfohlene Startdosis beträgt 1 x 200mg/Tag. Avapritinib führte in beiden Studien zu Gesamtansprechraten von 75%, zu einer signifikanten Reduktion einer Vielzahl krankheitsassoziierter Befunde (z.B. Reduktion von Knochenmarkinfiltration, Serum-Tryptase, Splenomegalie, KIT D816V Mutationslast) und zu einer signifikanten Verbesserung der krankheitsassoziierten Symptome und der Lebensqualität. Insgesamt erreichten 36% (EXPLORER) und 19% (PATHFINDER) der Pat. eine komplette Remission bzw. eine komplette Remission mit inkompletter Normalisierung des Blutbildes. Des Weiteren zeigte sich in beiden Studien, eine signifikante (>50%ige) Reduktion der Mastzellinfiltration im Knochenmark und der Mastzelltryptase im Serum sowie der *KIT* D816V Mutationslast. Die Verbesserung der Krankheitsaktivitätsparameter übersetzte sich ferner in ein verbessertes Symptombild gemessen mittels standardisierter Fragebogenanalysen (AdvSM-SAF).

Gelegentlich werden/wurden in der Erstlinientherapie auch andere Therapieoptionen wie das nicht zugelassene Cladribin, sehr viel seltener Interferon-alpha und andere, bei myeloischen Neoplasien häufig eingesetzte Substanzen, z.B. Hydroxyurea eingesetzt. Bei diesen Pat. ist in der Zweitlinientherapie auch eine Therapie mit Midostaurin möglich [].

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Standard nach Vortherapie mit Midostaurin ist die Gabe von Avapritinib. Ausnahmen sind selten.

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