

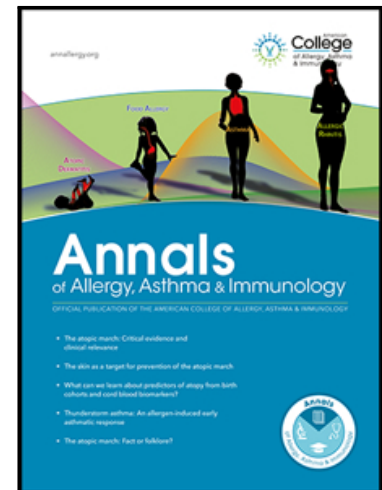
Treatment of Systemic Mastocytosis: Novel and Emerging therapies

Matthew P. Giannetti MD

PII: S1081-1206(21)00485-3
DOI: <https://doi.org/10.1016/j.anai.2021.06.021>
Reference: ANAI 3645

To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 31 March 2021
Revised date: 3 June 2021
Accepted date: 28 June 2021



Please cite this article as: Matthew P. Giannetti MD , Treatment of Systemic Mastocytosis: Novel and Emerging therapies, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.06.021>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Treatment of Systemic Mastocytosis: Novel and Emerging therapies

Author:

*Matthew P. Giannetti, MD,^{1,2}

¹Division of Allergy and Clinical Immunology, Brigham and Women's Hospital, Boston, MA; ²Harvard Medical School, Boston, MA;

Corresponding Author:

Matthew P. Giannetti, MD
Division of Allergy and Clinical Immunology
Brigham and Women's Hospital
60 Fenwood Road
Hale building for transformational medicine, 5th floor
Boston, MA 02132
Tel: 617 732-9850
Email: mgiannetti@bwh.harvard.edu

Conflict of Interest Disclosure:

Matthew Giannetti receives research and salary support from Blueprint Medicines (manufacturer of Avapritinib).

Funding Source: None

Key Words:

Mastocytosis, systemic mastocytosis, tyrosine kinase inhibitors, tryptase, KIT D816V

Abbreviations:

SM: Systemic Mastocytosis
ISM: Indolent systemic mastocytosis
SSM: smoldering systemic mastocytosis
SM-AHN: systemic mastocytosis with associated hematologic neoplasm
ASM: aggressive systemic mastocytosis
MCL: Mast cell leukemia
MC: Mast cell
TKI: Tyrosine Kinase Inhibitor
IL: Interleukin

Objective:

Systemic mastocytosis (SM) is a myeloproliferative disorder characterized by symptoms of mast cell (MC) activation and/or organ dysfunction related to MC tissue accumulation. Treatment of this condition is evolving as our understanding of the pathophysiology of the disease advances. This paper aims to highlight novel and experimental therapies for SM.

Data Sources:

PubMed literature search and ClinicalTrials.gov.

Study Selections:

Peer-reviewed studies involving therapies for SM were included. There was a particular focus on preclinical and clinical trial studies.

Results:

SM presents with a wide range of symptoms including symptoms of mast cell activation such as anaphylaxis, urticaria, diarrhea as well as organ failure secondary to aggressive tissue infiltration. Treatment of the disease is dependent on the variant; patients with aggressive disease warrant advanced therapies and a higher tolerance of adverse effects. As our understanding of the disease has advanced, several novel therapeutic options have emerged. These include tyrosine kinase inhibitors directed at the KIT protein and targeted monoclonal antibodies which decrease MC activation or reduce mast cell burden. There are a variety of new medications under development which will revolutionize treatment for patients with SM.

Conclusion:

Current treatment options for SM have inherent limitations and, in many cases, unacceptable side effects. As our molecular understanding of the disease advances, novel and experimental therapies are changing treatment paradigms of the disease.

Introduction:

Mast cells (MC) are tissue resident granulocytes that play a critical role in host defense.

They are armed with a variety of innate receptors and serve to identify danger and alert the immune system.¹ Disorders involving mast cells primarily occur due to accumulation of mast cells and/or excessive activation of MCs.²

Mastocytosis is a myeloproliferative disorder characterized by accumulation of MCs in various organs.³ The disease is driven by activating mutations in the KIT protein – classically KIT p.D816V.⁴ Mastocytosis is divided into cutaneous and systemic forms. Systemic mastocytosis has multiple subtypes (variants) classified by degree of organ infiltration. Disease severity ranges from indolent systemic mastocytosis which is associated with an normal life expectancy to mast cell leukemia which is invariably fatal at present.⁵

In non-advanced variants, symptoms of mastocytosis are related to direct activation of MCs and release of mediators.⁶ MCs release a variety of bioactive mediators including tryptase, histamine, prostaglandins, leukotrienes, and many others.⁷ Several mediators such as tryptase and histamine are preformed, while others such as prostaglandin are rapidly synthesized from arachidonic acid upon MC activation.⁸ In the case of advanced SM, symptoms such as organ failure are related to increased burden and tissue infiltration of MCs.⁹

For many years, treatment of mastocytosis was largely symptomatic and focused on mediator-release related symptoms. Treatment of the advanced variants of mastocytosis include anti-mediator therapy and cytoreductive therapy due to the mortality associated with MC infiltration and organ dysfunction/failure. However, standard therapy does not eliminate symptoms in many patients. Further, cytoreductive therapy does not sufficiently target MCs and is associated with side effects which may

be unacceptable to many patients. There is clearly an unmet need for targeted therapies with a favorable side effect profile.

Our understanding of the molecular and pathophysiologic characteristics of mastocytosis is rapidly advancing. This has led to the development of multiple targeted therapies which are revolutionizing treatment of mast cell disorders. This review aims to summarize current and novel therapies with a particular focus on medications poised to advance SM treatment paradigms.

Diagnosis and classification of systemic mastocytosis

Prior to discussion of therapies, a brief review of SM diagnostic criteria and variants is warranted. In general, mastocytosis is classified as cutaneous or systemic. Diagnosis of SM requires a bone marrow biopsy for histopathologic and molecular characterization. Table 1A describes the diagnostic criteria for systemic mastocytosis and table 1B describes criteria for subtypes.

Accurate diagnosis is essential as treatment varies considerably across subtype. For example, advanced SM variants are associated with significantly reduced life expectancy and warrant aggressive treatment and higher tolerance for adverse effects.⁵ Indolent SM is associated with a normal life expectancy and therefore, therapies with significant toxicity are not acceptable to most patients. This review will discuss therapies for all forms of systemic mastocytosis encompassing indolent systemic mastocytosis (ISM), smoldering systemic mastocytosis (SSM) as well as the advanced variants such

as systemic mastocytosis with associated hematologic neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL).

Current treatment options

Treatment can be conceptually divided into two categories: anti-mediator therapy and cytoreductive therapy. Anti-mediator therapy aims to inhibit bioactive mediators produced by MCs.⁹ Figure 1 depicts several of the major bioactive mediators produced by activated MCs. The goal of cytoreductive therapy is to rapidly reduce the tissue burden or quantity of MCs.

Anti-mediator therapy is important for treatment of all variants mastocytosis. Symptoms in non-advanced variants (CM, ISM, SSM) are driven largely by mast cell activation and anti-mediator therapy alone is sufficient. In advanced variants, anti-mediator therapy is used concurrently with cytoreduction.

The mainstay of therapy is oral H₁- and H₂-antagonists. Histamine release directly leads to cardiovascular, gastrointestinal, and cutaneous symptoms.^{10,11} Patients with mastocytosis have increased histamine metabolites in the blood and urine.⁸ Blockade of H₁ and H₂ receptors diminishes these symptoms; H₁- H₂-antagonists have a synergistic effect.¹¹ For these reasons, treatment with antihistamines are the mainstay of therapy for all forms of mastocytosis.

There is also data to support the use of montelukast¹² and oral cromolyn¹³. Montelukast is a cysteinyl leukotriene receptor antagonist. Mast cell activation is a stimulus for CysLT release, and patients with mastocytosis overproduce leukotrienes.¹⁴ One case report highlights improvement in cutaneous and pulmonary symptoms.¹² Oral Cromolyn is termed a mast cell 'stabilizer' although the mechanism of action is poorly understood.¹⁵ The medication is poorly absorbed and it is most helpful for gastrointestinal symptoms. Additional medications such as ketotifen¹⁶ and aspirin have been utilized. Ketotifen has been reported to control cutaneous and gastrointestinal symptoms.^{16,17} Aspirin is an irreversible cyclooxygenase inhibitor and reduces prostaglandin production.¹⁸ This may improve cutaneous and/or systemic symptoms in some patients.¹⁹ Of note, aspirin (and NSAIDs) should be used with caution in patients with systemic mastocytosis as it may precipitate systemic reactions.

Omalizumab is also used for myriad symptoms in mastocytosis and has a favorable safety profile. Data supports the use to prevent anaphylaxis and reduce gastrointestinal and cutaneous symptoms.^{20,21} It also may be used in patients with life-threatening anaphylaxis to hymenoptera venom and to achieve tolerance in patients with systemic adverse reactions during hymenoptera venom immunotherapy.^{22,23} However, placebo controlled studies are needed to validate the above findings.

As above, symptomatic treatment is useful for all patients with mastocytosis. However, some patients with extensive mast cell tissue infiltration need cytoreduction to remove

mast cell infiltrates and prevent/reverse organ failure. There are a handful of drugs that have data to support use in advanced variants of mastocytosis.

Cladribine has historically been considered first-line therapy for advanced variants of systemic mastocytosis. Cladribine is a purine analog antimetabolite and inhibits the synthesis of DNA. Most patients will have a decrease in serum tryptase, reduction of bone marrow MCs and improvement in cutaneous lesions.²⁴ Approximately 30% of patients will have a major response, defined by more than 50% improvement in the above categories.²⁵ However, many patients will relapse after treatment and develop resistance to future cladribine treatment.²⁶ This therapy is often complicated by dose-limiting toxicity including cytopenia, fever, nausea/vomiting/diarrhea, and neuropathy.

Several other therapies have also been used in mastocytosis. Imatinib is useful in cases with non-kinase domain (non-D816V) mutations.^{27,28} The D816V mutation confers resistance to imatinib and the vast majority of patients with systemic mastocytosis carry the D816V mutation.⁴ Therefore, D816V must be definitively excluded using a high-sensitivity PCR-based assay before considering therapy with imatinib. Response rates of up to 50% have been reported for patients without D816V mutations.²⁹ Imatinib side effects include myelosuppression, edema, and gastrointestinal symptoms. Interferon-alpha is primarily used for patients with refractory symptoms who are not candidates for cytoreductive therapies. It is often administered concurrently with prednisone to reduce side effects and enhance response. Reported responses vary; 19-63% of patients have

a partial response.^{25,30} The therapy is limited by severe side effects including fatigue and mood disorders.³⁰

Novel and experimental therapeutics

Several novel therapies are currently under or awaiting investigation in patients with SM. Therapeutic targets include extracellular proteins as well as intracellular portions of the KIT protein. Medications in the following section are divided by mechanism of action: monoclonal antibodies and small molecule inhibitors. Table 2 highlights drug candidates, target, and mechanism of action.

Tyrosine Kinase Inhibitors

Most patients with systemic mastocytosis have activating mutations in the KIT protein.^{31,32} The most common mutation is p.KIT D816V.⁴ This mutation often occurs at low allele frequencies and testing via a PCR-based modality is significantly more sensitive than a 'next-generation sequencing' platform.³³ Testing for D816V in peripheral blood via PCR is sensitive and detects up to 94% of patients with mastocytosis, including those with baseline tryptase <20ng/mL.³⁴

The high rate of activating KIT mutations in systemic mastocytosis has led to multiple therapies targeting the KIT protein. KIT is a receptor tyrosine kinase (RTK) and the receptor for stem cell factor.³⁵ Medications targeting KIT (or other RTKs) are broadly referred to as tyrosine kinase inhibitors (TKI). TKIs can be categorized into five categories based on mechanism of action. Discussion of categories are outside the

scope of this review. Multiple TKIs are under investigation for mastocytosis. Therapeutic response is often reported as a response rate; this is not directly comparable across drugs as studies used different response rate criteria.

Midostaurin:

Midostaurin is a multi-kinase inhibitor which was approved in 2017 for aggressive systemic mastocytosis, systemic mastocytosis with associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).³⁶ Approval was based on an open-label study involving 116 patients with advanced variants of mastocytosis. The overall response rate (major response + partial response) was 60% and the medication decreased bone marrow mast cell burden, serum tryptase level, and spleen volume in more than 70% of patients.³⁶ Midostaurin has also been shown to improve quality of life in advanced systemic mastocytosis.³⁷

Midostaurin has also been used in patients with ISM. A small phase 2 trial of 20 patients reported an improvement in symptoms scores and reduction in baseline serum tryptase.³⁸ Midostaurin does have significant toxicity – nausea was reported in 79% of subjects. It may also cause bone marrow suppression and must be used with caution.³⁶

Avapritinib:

Avapritinib is a small molecule drug designed to target human tyrosine kinases including KIT and PDGFRA. The medication is highly selective for the KIT D816V mutation. Avapritinib is currently under investigation for diseases driven by activating KIT

mutations including mastocytosis and Gastrointestinal stromal tumors (GIST).

Avapritinib received FDA approval for adults with unresectable GIST tumors and PDGFRA exon 18 mutations in January 2020.³⁹

There are several studies underway in patients with mastocytosis. The Explorer trial was a phase 1 trial involving patients with advanced SM and reported an overall response rate (ORR) of 77%.⁴⁰ A phase II trial (Pathfinder) is currently enrolling patients with advanced variants of SM.⁴¹ The PIONEER trial is a phase 2 study investigating the use of Avapritinib in patients with indolent systemic mastocytosis.⁴² Endpoints include a composite symptom score (primary) as well as tryptase, bone marrow MC, and D816V allele fraction changes (secondary). Initial data report a significant mean % reduction in symptom scores vs. placebo (at recommended dose of 25mg). 70% of patients also showed a >50% reduction in baseline serum tryptase.⁴³ Further, data derived from skin biopsy shows reduction in cutaneous mast cells after 12 weeks of therapy which is promising for the treatment of cutaneous lesions in systemic mastocytosis.⁴⁴

Masitinib

Masitinib is a multi-kinase inhibitor with an affinity for Src family kinases such as LYN and FYN. Notably, the medication has a higher affinity for wild-type KIT compared to D816V-mutated KIT. It is therefore, advocated primarily as a treatment to improve quality of life rather than preferentially eliminated D816V-bearing MCs.

Phase 2 data from 2010 show an overall response rate in 14/25 (56%) of patients.⁴⁵ A larger, placebo-controlled, phase 3 study was published in 2017.⁴⁶ enrolled 135 patients across 15 countries. 18.7% of patients showed a major response (defined as >75% improvement from baseline) in pruritus, flushing, depression, or fatigue.⁴⁶ The medication was very well tolerated with diarrhea (4%) and urticaria (2%) as the major side effects.

PLX9486:

PLX9486 is a selective tyrosine-kinase inhibitor with activity against activating KIT mutations.⁴⁷ In vitro data shows potent growth inhibition of BaF3 cells bearing the D816V mutation. An animal xenograft model also shows the ability to reduce tumor burden in a model involving activating KIT mutations. There is no human data regarding PLX9486 in mastocytosis. It has been used in a single phase I/II study for GIST with positive results.

Ripretinib

Ripretinib (DCC-2618) is a 'switch-control' type II inhibitor which has biologic activity across several receptor tyrosine kinases including PDGFR α and KIT.⁴⁸ It 'locks' the KIT protein into an inactive, non-signaling state. This prevents KIT signal transduction and downstream MC activation.

In vitro, the drug shows broad efficacy against neoplastic human MCs derived from patients with ASM and MCL.⁴⁹ It induces apoptosis in neoplastic MCs, inhibits

phosphorylation of downstream targets, and decreased mediator release after IgE-mediated activation.⁴⁹ It has also shown potency against multmutated SM and several different activating exon 17 mutations.⁵⁰ Ripretinib is currently in phase 3 trials for Gastrointestinal Stromal Tumor (GIST). There is a registered trial for mastocytosis, but the study is not actively recruiting.

Monoclonal antibodies

Tagraxofusp (SL-401)

Tagraxofusp is an engineered molecule composed of diphtheria toxin covalently attached a portion of the IL-3 cytokine. The drug binds to the β -chain of the IL-3 receptor (CD123) which mediates endocytosis.⁵¹ The diphtheria toxin is subsequently released and induces cytotoxicity via protein inhibition.⁵² A small preclinical cohort of patients with SM show CD123 expression on 61% of patients with ISM and 100% on those with ASM.⁵³ Major side effects include cytopenia and marrow suppression.⁵⁴ There are several ongoing trials with this candidate in leukemia and advanced hematologic malignancies although none involving systemic mastocytosis.

Lirentelimab (AK002)

Lirentelimab is a humanized IgG1 monoclonal antibody directed at Siglec-8. Siglec-8 is expressed primarily on mast cells and eosinophils and this medication has been studied in both contexts. A small phase 1 study involving 12 patients was reported in 2019.⁵⁵ Patients noted an improvement in skin gastrointestinal, neurologic, and musculoskeletal

symptoms. There was a statically significant improvement in quality of life across three different patient reported outcome (PRO) scores.⁵⁵

Preclinical data shows that the medication can inhibit IgE-dependant mast cell activation and anaphylaxis.^{56,57} The medication also shows positive data for eosinophilic gastrointestinal diseases and chronic spontaneous urticaria.⁵⁸ A phase 2 study (ENIGMA) showed positive data in patients with eosinophilic gastroenteritis and/or eosinophilic duodenitis.⁵⁸ There is also an ongoing study in eosinophilic esophagitis. Currently, there are no ongoing trials in patients with mast cell disorders.

CDX-0159

CDX-0159 is a humanized IgG1 monoclonal antibody directed at the KIT protein.⁵⁹ Data from healthy human volunteers shows a reduction in serum tryptase levels after approximately one week of therapy (depending on dose).⁵⁹ Studies in chronic spontaneous urticaria are currently underway. There are no currently enrolling trials for patients with mast cell disorders.

Areas of unmet need and future study

The most pressing need is for therapeutic options in patients with ISM and refractory symptoms. Current treatment of mastocytosis is sharply divided by the subtype. Non-advanced forms (ISM, SSM) are treated exclusively with anti-mediator therapy. Advanced forms are often treated with cytoreduction although the side effect profile of

many cytoreductive therapies is unacceptable for most patients with ISM.⁶⁰ As such, TKI or cytoreductive therapy with a favorable side effect profile is a significant need.

Second, there exists a need for therapies (such as omalizumab) that are not directly cytotoxic (cytoreductive) but decrease MC activation. Omalizumab has utility in treatment of mastocytosis although is not sufficient in many cases. Other monoclonal antibodies have a similar side effect profile but are not yet available for clinical trials or routine use.

Treatment of cutaneous lesions is also a significant unmet need. Up to 90% of patients with ISM have cutaneous lesions and the stigmata of CM is deleterious to quality of life.^{31,61} A topical therapy capable of reduction of cutaneous MCs would be helpful to reduce both cutaneous symptoms and appearance of the disease without subjecting patients to toxic systemic therapy. Although not discussed in this review, this is particularly important for children with extensive maculopapular CM and diffuse cutaneous mastocytosis. It is noted that most children with cutaneous disease undergo spontaneous resolution and the above therapies would be employed for symptom control.

Conclusion

Systemic mastocytosis is a myeloproliferative characterized by tissue expansion of mast cells and symptoms related to mast cell activation. Treatment has classically involved blockade of mast cell mediators and cytoreductive therapy for advanced variants of the

disease. However, these treatments are limited by insufficient symptom improvement and unacceptable toxicity. Novel targeted therapies are currently under investigation that manipulate key pathways of mast cell activation and proliferation. Early data are promising and may change the future treatment of mastocytosis. However, despite recent advances and emerging therapeutics, there is still considerable unmet need for treatment of patients with systemic mastocytosis.

Learning Objectives: At the conclusion of this activity, participants should be able to:

- Summarize diagnosis and current treatment for systemic mastocytosis as well as the limitations of current therapy
- Discuss novel treatment strategies such as tyrosine kinase inhibitors and the mechanism of action of novel therapies.

Q1. Which of the following is the major diagnostic criterion for systemic Mastocytosis (SM)?

- A. CD2 Expression on bone marrow mast cells
- B. Maculopapular cutaneous lesions
- C. Presence of KIT D816V mutation
- D. Aggregates of 15 or more mast cells in the bone marrow
- E. Tryptase greater than 20ng/mL

Q1 ANS: D. Aggregates of greater than 15 MCs in the bone marrow

Rationale:

The major criteria for SM is 'Multifocal dense infiltrates of MCs (>15 MCs) in bone marrow biopsies or other extracutaneous organs.' Option A, C, and E are all minor criteria for SM diagnosis. Formal diagnosis requires one major and one minor criteria or three minor criterion.

References:

1. Valent P, Akin C, Metcalfe DD. Review Article Mastocytosis : 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420-1428. doi:10.1182/blood-2016-09-731893.

Q2. Systemic mastocytosis is divided into subtypes or ‘variants.’ Which of the following is a non-advanced variant of SM?

- A. Mast cell leukemia
- B. Indolent systemic mastocytosis
- C. Cutaneous mastocytosis
- D. Systemic mastocytosis with associated hematologic neoplasm
- E. Aggressive systemic mastocytosis

Q2 ANS: B. Indolent Systemic Mastocytosis.

Rationale:

Indolent systemic mastocytosis and smoldering systemic mastocytosis are the non-advanced variants of SM. The other options are advanced variants (MCL, SM-AHN, and ASM) or not systemic mastocytosis (cutaneous mastocytosis). Proper classification and diagnosis is important as life expectancy depends upon the variant.

References:

1. Valent P, Akin C, Metcalfe DD. Review Article Mastocytosis : 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420-1428. doi:10.1182/blood-2016-09-731893.

Q3. Tyrosine Kinase Inhibitors have emerged as a major therapeutic class of medications for systemic mastocytosis. These medications target which molecule?

- A. Histamine
- B. Tryptase
- C. KIT
- D. Prostaglandins
- E. Leukotrienes

Q3 ANS: C. KIT

Rationale:

Tyrosine Kinase Inhibitors (TKIs) block signaling through the KIT protein which is a receptor tyrosine kinase. This protein is the receptor for stem cell factor and is critical for mast cell growth and differentiation. Midostaurin is the only FDA approved TKI although several drugs are currently in clinical trials.

References:

1. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26):2530-2541. doi:10.1056/NEJMoa1513098
2. Akin C, Oude Elberink H, Gotlib JR, et al. PIONEER part 2: a randomized, double-blind, place-controlled, phase2 study to evaluate safety and efficacy of avapritinib in indolent systemic mastocytosis. *Am Soc Hematol*. Published online 2020.

Q4. This class of medications is used for all types of systemic mastocytosis

- A. Midostaurin
- B. Cladribine
- C. Hydroxyurea
- D. Interferon-alpha
- E. H₁-antihistamines

Q4 ANS: E. H₁-antihistamines

Rationale:

H₁-antihistamines as well as other anti-mediator therapies are useful for all types of mastocytosis. They are low-risk interventions and reduce symptoms related to mast cell activation. Midostaurin, cladribine, and hydroxyurea are cytoreductive therapies and used only in the advanced variants of mastocytosis. Interferon-alpha has considerable side effects and is used only in select cases with severe symptoms.

References:

1. Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. *N Engl J Med*. 2015;373(2):163-172. doi:10.1056/NEJMra1409760

Q5. Which of the following is true about current therapies used to treat systemic mastocytosis?

- A. They are universally effective
- B. H₁-antihistamines effectively reduce mast cell burden
- C. They are not universally effective and/or have unacceptable side effects
- D. Cladribine is effective for patients with indolent systemic mastocytosis
- E. There are not therapies targeting the KIT protein.

Q5 ANS: C. They are not universally effective and/or have unacceptable side effects

Rationale:

Treatment for mastocytosis is hampered by limited efficacy and/or unacceptable side effects. Therapies are not universally effective. H₁-antihistamines block histamine, they do not reduce mast cell burden. Cladribine is used exclusively in advanced variants. Tyrosine kinase inhibitors block KIT protein signaling.

References:

1. Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of mastocytosis: Current status and outlook toward the future. *Cancer Res.* 2017;77(6):1261-1270. doi:10.1158/0008-5472.CAN-16-2234
2. Bibi S, Langenfeld F, Jeanningros S, et al. Molecular defects in mastocytosis: KIT and beyond KIT. *Immunol Allergy Clin North Am.* 2014;34(2):239-262. doi:10.1016/j.iac.2014.01.009

References

1. Olivera A, Beaven MA, Metcalfe DD. Mast cells signal their importance in health and disease. *J Allergy Clin Immunol.* 2018;142(2):381-393. doi:10.1016/j.jaci.2018.01.034
2. Valent P, Akin C, Bonadonna P, et al. Proposed Diagnostic Algorithm for Patients with Suspected Mast Cell Activation Syndrome. *J Allergy Clin Immunol Pract.* 2019;7(4):1125-1133.e1. doi:10.1016/j.jaip.2019.01.006

3. Valent P, Akin C, Metcalfe DD. Review Article Mastocytosis : 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420-1428. doi:10.1182/blood-2016-09-731893.effective
4. Bibi S, Langenfeld F, Jeanningros S, et al. Molecular defects in mastocytosis: KIT and beyond KIT. *Immunol Allergy Clin North Am*. 2014;34(2):239-262. doi:10.1016/j.iac.2014.01.009
5. Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol*. 2014;166(4):521-528. doi:10.1111/bjh.12916
6. Theoharides TC, Valent P, Akin C. Mast Cells, Mastocytosis, and Related Disorders. *N Engl J Med*. 2015;373(2):163-172. doi:10.1056/NEJMra1409760
7. Valent P, Akin C, Hartmann K, et al. Mast cells as a unique hematopoietic lineage and cell system: From Paul Ehrlich's visions to precision medicine concepts. *Theranostics*. 2020;10(23):10743-10768. doi:10.7150/thno.46719
8. Butterfield J, Weiler CR. The Utility of Measuring Urinary Metabolites of Mast Cell Mediators in Systemic Mastocytosis and Mast Cell Activation Syndrome. *J Allergy Clin Immunol Pract*. 2020;8(8):2533-2541. doi:10.1016/j.jaip.2020.02.021
9. Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of mastocytosis: Current status and outlook toward the future. *Cancer Res*. 2017;77(6):1261-1270. doi:10.1158/0008-5472.CAN-16-2234
10. Vigorito C, Russo P, Picotti G, Chiariello M, Poto S, Marone G. Cardiovascular Effects of Histamine Infusion in Man. *J Cardiovasc Pharmacol*. 1983;5:531-537.
11. Kaliner M, Sigler R, Summers R, Shelhamer JH. Effects of infused histamine:

- analysis of the effects of H-1 and H-2 histamine receptor antagonists on cardiovascular and pulmonary responses. *J Allergy Clin Immunol.* 1981;68(5):365-371. doi:10.1016/0091-6749(81)90134-2
12. Tolar J, Tope WD, Neglia JP. Leukotriene-Receptor Inhibition for the Treatment of Systemic Mastocytosis. *N Engl J Med.* 2004;350(7):735-736. doi:10.1056/nejm200402123500723
13. Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol.* 1990;85(5):852-855. doi:10.1016/0091-6749(90)90067-E
14. Butterfield JH. Increased leukotriene E4 excretion in systemic mastocytosis. *Prostaglandins Other Lipid Mediat.* 2010;92(1-4):73-76. doi:10.1016/j.prostaglandins.2010.03.003
15. Correia I, Wang L, Pang X, Theoharides TC. Characterization of the 78 kDa mast cell protein phosphorylated by the antiallergic drug cromolyn and homology to moesin. *Biochem Pharmacol.* 1996;52(3):413-424. doi:10.1016/0006-2952(96)00243-2
16. PÓVOA P, DUCLA-SOARES J, FERNANDES A, PALMA-CARLOS AG. A case of systemic mastocytosis; therapeutic efficacy of ketotifen. *J Intern Med.* 1991;229(5):475-477. doi:10.1111/j.1365-2796.1991.tb00379.x
17. Ting S. Ketotifen and systemic mastocytosis. *J Allergy Clin Immunol.* 1990;85(4):818. doi:10.1016/0091-6749(90)90205-I
18. Butterfield JH. Survey of aspirin administration in systemic mastocytosis. *Prostaglandins Other Lipid Mediat.* 2009;88(3-4):122-124.

doi:10.1016/j.prostaglandins.2009.01.001

19. Butterfield JH, Weiler CR. Prevention of mast cell activation disorder-associated clinical sequelae of excessive prostaglandin D2 production. *Int Arch Allergy Immunol*. 2008;147(4):338-343. doi:10.1159/000144042
20. Carter MC, Robyn JA, Bressler PB, Walker JC, Shapiro GG, Metcalfe DD. Omalizumab for the treatment of unprovoked anaphylaxis in patients with systemic mastocytosis. *J Allergy Clin Immunol*. 2007;119(6):1550-1551. doi:10.1016/j.jaci.2007.03.014
21. Broesby-Olsen S, Vestergaard H, Mortz CG, et al. Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: Efficacy and safety observations. *Allergy Eur J Allergy Clin Immunol*. 2018;73(1):230-238. doi:10.1111/all.13237
22. Giannetti M, Silver J, Hufdhi R, Castells M. One-day ultrarush desensitization for Hymenoptera venom anaphylaxis in patients with and without mast cell disorders with adjuvant omalizumab. *J Allergy Clin Immunol Pract*. 2020;8(4):1431-1435.e3. doi:10.1016/j.jaip.2019.10.022
23. Sokol KC, Ghazi A, Kelly BC, Grant JA. Omalizumab as a Desensitizing Agent and Treatment in Mastocytosis: A Review of the Literature and Case Report. *J Allergy Clin Immunol Pract*. 2014;2(3):266-270. doi:10.1016/j.jaip.2014.03.009
24. Kluin-Nelemans HC, Oldhoff JM, Van Doormaal JJ, et al. Cladribine therapy for systemic mastocytosis. *Blood*. 2003;102(13):4270-4276. doi:10.1182/blood-2003-05-1699
25. Lim KH, Pardanani A, Butterfield JH, Li CY, Tefferi A. Cytoreductive therapy in

108 adults with systemic mastocytosis: Outcome analysis and response prediction during treatment with interferon-alpha, hydroxyurea, imatinib mesylate or 2-chlorodeoxyadenosine. *Am J Hematol*. 2009;84(12):790-794.
doi:10.1002/ajh.21561

26. Aichberger KJ, Sperr WR, Gleixner K V., Kretschmer A, Valent P. Treatment responses to cladribine and dasatinib in rapidly progressing aggressive mastocytosis. *Eur J Clin Invest*. 2008;38(11):869-873. doi:10.1111/j.1365-2362.2008.02036.x
27. Akin C, Fumo G, Yavuz AS, Lipsky PE, Neckers L, Metcalfe DD. A novel form of mastocytosis associated with a transmembrane c-kit mutation and response to imatinib. *Blood*. 2004;103(8):3222-3225. doi:10.1182/blood-2003-11-3816
28. Vega-Ruiz A, Cortes JE, Sever M, et al. Phase II study of imatinib mesylate as therapy for patients with systemic mastocytosis. *Leuk Res*. 2009;33(11):1481-1484. doi:10.1016/j.leukres.2008.12.020
29. Pardanani A, Elliott M, Reeder T, et al. Imatinib for systemic mast-cell disease. *Lancet*. 2003;362(9383):535-537. doi:10.1016/S0140-6736(03)14115-3
30. Casassus P, Caillat-Vigneron N, Martin A, et al. Treatment of adult systemic mastocytosis with interferon- α : Results of a multicentre phase II trial on 20 patients. *Br J Haematol*. 2002;119(4):1090-1097. doi:10.1046/j.1365-2141.2002.03944.x
31. Álvarez-Twose I, González de Olano D, Sánchez-Muñoz L, 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(6).

doi:10.1016/j.jaci.2010.02.019

32. Berezowska S, Flaig MJ, Ruëff F, et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. *Mod Pathol*. 2014;27(1):19-29.
doi:10.1038/modpathol.2013.117
33. George TI, Hoehn G, Lin H-M, Miller S, Akin C. Increased Detection of KIT D816V Mutation in Peripheral Blood Samples from Patients with Indolent Systemic Mastocytosis (ISM) in the Phase 2 Pioneer Study Using a High Sensitivity Droplet Digital (dd) PCR Assay Compared with Next Generation Sequencing (NG. *Blood*. 2020;136(Supplement 1).
34. Kristensen T, Vestergaard H, Bindslev-Jensen C, Møller MB, Broesby-Olsen S. Sensitive KIT D816V mutation analysis of blood as a diagnostic test in mastocytosis. *Am J Hematol*. 2014;89(5):493-498. doi:10.1002/ajh.23672
35. Lennartsson J, Ronnstrand L. Stem Cell Factor Receptor/c-Kit: From Basic Science to Clinical Implications. *Physiol Rev*. 2012;92(4):1619-1649.
doi:10.1152/physrev.00046.2011
36. Gotlib J, Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. *N Engl J Med*. 2016;374(26):2530-2541.
doi:10.1056/NEJMoa1513098
37. Hartmann K, Gotlib J, Akin C, et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. *J Allergy Clin Immunol*. 2020;146(2):356-366.e4. doi:10.1016/j.jaci.2020.03.044
38. van Anrooij B, Oude Elberink JNG, Span LFR, et al. Midostaurin in patients with indolent systemic mastocytosis: An open-label phase 2 trial. *J Allergy Clin*

Immunol. 2018;142(3):1006-1008.e7. doi:10.1016/j.jaci.2018.06.003

39. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. *Lancet Oncol.* 2020;21(7):935-946. doi:10.1016/S1470-2045(20)30269-2
40. Deininger MW, Gotlib JR, Robinson WA, et al. Clinical activity in a phase 1 study of BLU-285, a potent, highly-selective inhibitor, of KIT D816V in advanced systemic mastocytosis (AdVSM). *Blood.* 2017;130(Supplement 1):2-2.
41. (PATHFINDER) Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, in Patients With Advanced Systemic Mastocytosis. NCT03580655. Clinicaltrials.gov
42. Akin C, Oude Elberink H, Gotlib JR, et al. PIONEER part 2: a randomized, double-blind, place-controlled, phase 2 study to evaluate safety and efficacy of avapritinib in indolent systemic mastocytosis. *Am Soc Hematol.* Published online 2020.
43. Akin C, Oude Elberink H, Gotlib JR, et al. Results from Pioneer: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Avapritinib in Patients with Indolent Systemic Mastocytosis. *ASH Annu Meet.* Published online 2020.
44. George TI, Broesby-Olsen S, Wada D, et al. Changes in mast cell numbers and phenotype in patients with indolent systemic mastocytosis treated with avapritinib. *AACR Annu Meet.* Published online 2021.
45. Paul C, Sans B, Suarez F, et al. Masitinib for the treatment of systemic and cutaneous mastocytosis with handicap: A phase 2a study. *Am J Hematol.*

2010;85(12):921-925. doi:10.1002/ajh.21894

46. Lortholary O, Chandesris MO, Livideanu CB, et al. Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study. *Lancet*. 2017;389(10069):612-620. doi:10.1016/S0140-6736(16)31403-9
47. Gebreyohannes YK, Burton EA, Wozniak A, et al. PLX9486 shows anti-tumor efficacy in patient-derived, tyrosine kinase inhibitor-resistant KIT-mutant xenograft models of gastrointestinal stromal tumors. *Clin Exp Med*. 2019;19(2):201-210. doi:10.1007/s10238-018-0541-2
48. Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants. *Cancer Cell*. 2019;35(5):738-751.e9. doi:10.1016/j.ccell.2019.04.006
49. Schneeweiss M, Peter B, Bibi S, et al. The KIT and PDGFRA switch-control inhibitor DCC-2618 blocks growth and survival of multiple neoplastic cell types in advanced mastocytosis. *Haematologica*. Published online 2018;haematol.2017.179895. doi:10.3324/haematol.2017.179895
50. Smith BD, Hood MM, Wise SC, et al. Abstract 2690: DCC-2618 is a potent inhibitor of wild-type and mutant KIT, including refractory Exon 17 D816 KIT mutations, and exhibits efficacy in refractory GIST and AML xenograft models. *Cancer Res*. 2015;75(15 Supplement):2690 LP - 2690. doi:10.1158/1538-7445.AM2015-2690
51. Alkharabsheh O, Frankel AE. Clinical activity and tolerability of SL-401

- (Tagraxofusp): Recombinant diphtheria toxin and interleukin-3 in hematologic malignancies. *Biomedicines*. 2019;7(1). doi:10.3390/biomedicines7010006
52. Collier RJ. Diphtheria toxin: mode of action and structure. *Bacteriol Rev*. 1975;39(1):54-85. doi:10.1128/br.39.1.54-85.1975
53. Pardanani A, Reichard KK, Zblewski D, et al. CD123 immunostaining patterns in systemic mastocytosis: Differential expression in disease subgroups and potential prognostic value. *Leukemia*. 2016;30(4):914-918. doi:10.1038/leu.2015.348
54. Patnaik MM, Gupta V, Gotlib JR, et al. Results from Ongoing Phase 2 Trial of SL-401 in Patients with Advanced, High-Risk Myeloproliferative Neoplasms Including Chronic Myelomonocytic Leukemia. *Blood*. 2016;128(22):4245. doi:10.1182/blood.V128.22.4245.4245
55. Siebenhaar F, Bonnekoh H, Hawro T, et al. Safety and Efficacy Data of AK002, an Anti-Siglec-8 Monoclonal Antibody, in Patients with Indolent Systemic Mastocytosis (ISM): Results from a First-in-Human, Open-label Phase 1 Study. *Eur Acad Allergy Clin Immunol Annu Meet*. Published online 2019:LBTP1937.
56. Schanin J, Gebremeskel S, Korver W, et al. A monoclonal antibody to Siglec-8 suppresses non-allergic airway inflammation and inhibits IgE-independent mast cell activation. *Mucosal Immunol*. 2020;(June):1-11. doi:10.1038/s41385-020-00336-9
57. Youngblood BA, Brock EC, Leung J, et al. AK002, a Humanized Sialic Acid-Binding Immunoglobulin-Like Lectin-8 Antibody that Induces Antibody-Dependent Cell-Mediated Cytotoxicity against Human Eosinophils and Inhibits Mast Cell-Mediated Anaphylaxis in Mice. *Int Arch Allergy Immunol*. 2019;180(2):91-102.

doi:10.1159/000501637

58. Dellon ES, Peterson KA, Murray JA, et al. Anti–Siglec-8 Antibody for Eosinophilic Gastritis and Duodenitis. *N Engl J Med*. 2020;383(17):1624-1634.
doi:10.1056/nejmoa2012047
59. Maurer M, Murphy M, Hawthorne T, et al. CDX-0159, an anti-KIT monoclonal antibody, demonstrates dose-dependent reductions in plasma Tryptase and a favorable safety profile in a Phase 1a healthy volunteer study. *EAACI Annu Meet*. Published online 2020.
60. Stone RM, Manley PW, Larson RA, Capdeville R. Midostaurin: Its odyssey from discovery to approval for treating acute myeloid leukemia and advanced systemic mastocytosis. *Blood Adv*. 2018;2(4):444-453.
doi:10.1182/bloodadvances.2017011080
61. Jennings S, Russell N, Jennings B, et al. The mastocytosis society survey on mast cell disorders: Patient experiences and perceptions. *J Allergy Clin Immunol Pract*. 2014;2(1):70-76. doi:10.1016/j.jaip.2013.09.004

Systemic Mastocytosis			
Major	Minor	“B” Findings	“C” Findings
Aggregates of greater than 15 MCs	>25% of MCs have atypical, spindled morphology	1. Bone marrow biopsy showing >30% MCs and/or serum total tryptase level >200 ng/mL.	Bone marrow failure with one or more cytopenia (ANC <1 × 10 ⁹ /L, Hb <10 g/dL, or platelets <100 × 10 ⁹ /L)
	MC coexpression of CD2 and/or CD25	Signs of dysplasia or myeloproliferation in non-MC lineage(s) but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (SM-AHN)	Palpable hepatomegaly with impairment of liver function including ascites and/or portal hypertension.
	Baseline serum tryptase >20ng/mL	Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism	Skeletal involvement with large osteolytic lesions and/or pathologic fractures.
	Presence of KIT D816V		Palpable splenomegaly with hypersplenism.
			Malabsorption with weight loss due to MC infiltrates

Table 1A: World Health Organization diagnostic criteria for systemic mastocytosis and variants.³

Diagnostic criteria for SM are fulfilled by 1 major and 1 minor or 3 minor criteria. “B” and “C” findings are used to diagnosis variants (see table 1B).

SM Variant*	Diagnostic Criteria
Indolent Systemic Mastocytosis	No “B” or “C” findings
Smoldering systemic mastocytosis	Two “B” findings, no “C” findings
Advanced SM	
Aggressive systemic mastocytosis	One or more “C” finding
Mast cell leukemia	>20% MCs in the bone marrow aspirate or peripheral blood with diffuse marrow infiltration
Systemic mastocytosis with associated hematologic neoplasm	Fulfill diagnostic criteria for an associated myeloproliferative disorder

Table 1B: World Health Organization diagnostic criteria for advanced variants of mastocytosis

*Formal diagnostic criteria for SM must first be fulfilled before assigning a variant

Drug	Target	Class	Recent study and SM Variant
Tagraxofusp (SL-401)	IL-3	MAb	Preclinical ⁵³
Lirentelimab	Siglec-8	mAb	ISM: • Phase 1 ⁵⁵
Midostaurin	KIT	TKI	ASM: • Phase 3 ³⁶ • Post-approval ³⁷ ISM: • Phase 2 ³⁸
Avapritinib	KIT	TKI	ASM: • Phase 1 ⁴⁰ • Phase 2 ⁴¹ ISM: • Phase 2 ⁴²
Masitinib	KIT	TKI	ISM: • Phase 2 ⁴⁶
Ripretinib (DCC-2618)	KIT	TKI	Preclinical ⁴⁹
PLX9486		TKI	Preclinical ⁴⁷

Table 2: Novel and emerging drugs including drug target, class, and selected studies

Figures

Figure 1: Mast cell mediators

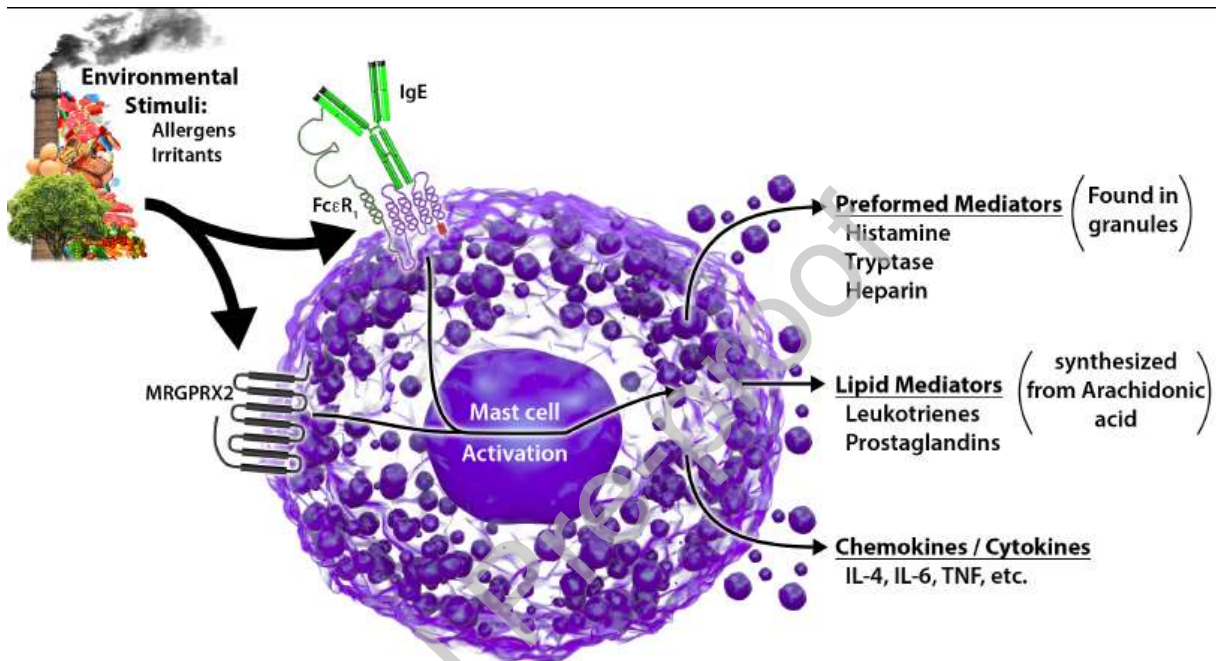


Figure 2: Mast cells and KIT protein: Targets of novel therapeutics

