Updates in Mastocytosis

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Professor of Pathology
<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosure</th>
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<tr>
<td>Research Support / Grants</td>
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<td>Stock/Equity (any amount)</td>
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<td>Other</td>
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</table>
Outline

• Classification
• Advanced mastocytosis
• A case report
• Clinical trials
• Other potential therapies
Outline

• Classification
• Advanced mastocytosis
• A case report
• Clinical trials
• Other potential therapies
Mastocytosis symposium and consensus meeting on classification and diagnostic criteria for mastocytosis
Boston, October 25-28, 2012
2008 WHO Classification Scheme for Myeloid Neoplasms

Acute Myeloid Leukemia

Myelodysplastic Syndromes

MDS/MPN

Myeloproliferative Neoplasms

Myeloid or lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1

Chronic Myelomonocytic Leukemia
Atypical Chronic Myeloid Leukemia
Juvenile Myelomonocytic Leukemia
MDS/MPN, unclassifiable

Chronic Myelogenous Leukemia

Polycythemia Vera
Essential Thrombocythemia
Primary Myelofibrosis

Chronic Neutrophilic Leukemia
Chronic Eosinophilic Leukemia, NOS
Hypereosinophilic Syndrome
Mast Cell Disease

MPNs, unclassifiable

Myeloid neoplasms associated with PDGFRα rearrangement
Myeloid neoplasms associated with PDGFRβ rearrangement
Myeloid neoplasms associated with FGFR1 rearrangement (EMS)
2017 WHO Classification Scheme for Myeloid Neoplasms

- Acute Myeloid Leukemia
- Myelodysplastic Syndromes
- MDS/MPN
- Myeloproliferative Neoplasms
- Mastocytosis
- Myeloid/lymphoid neoplasms with eosinophilia and gene rearrangement

- Chronic Myeloid Leukemia
- Atypical Chronic Myeloid Leukemia
- Juvenile Myelomonocytic Leukemia
- MDS/MPN with ring sideroblasts and thrombocytosis
- MDS/MPN, unclassifiable

- Chronic Myeloid Leukemia
- Polycythemia Vera
- Essential Thrombocythemia
- Primary Myelofibrosis

- Chronic Neutrophilic Leukemia
- Chronic Eosinophilic Leukemia, NOS
- MPN, unclassifiable

- Myeloid/lymphoid neoplasms with PDGFRα rearrangement
- Myeloid/lymphoid neoplasms with PDGFRβ rearrangement
- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
- Myeloid/lymphoid neoplasms with PCM1-JAK2 rearrangement

- Myeloid/lymphoid neoplasms with FGFR1 rearrangement
WHO 2008 definition of systemic mastocytosis

**Major:** Multifocal dense infiltrates of mast cells

**Minor:**
- >25% of mast cells with atypical morphology
- D816V *KIT* mutation
- CD25 and/or CD2
- Serum total tryptase >20 ng/mL
  (unless associated myeloid disorder)

WHO 2008 definition of systemic mastocytosis

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WHO 2017 definition of systemic mastocytosis

**Major:** Multifocal dense infiltrates of mast cells

**Minor:**
- >25% of mast cells with atypical morphology
- D816V *KIT* mutation
- CD25 *with or without* CD2
- Serum total tryptase >20 ng/mL
  (unless associated myeloid disorder)

WHO 2008 Classification of Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
  - Indolent systemic mastocytosis
  - Systemic mastocytosis with associated clonal, hematologic non-mast cell lineage disease
  - Aggressive systemic mastocytosis
  - Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytoma
WHO 2017 Classification of Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
  - Indolent systemic mastocytosis
  - Smoldering systemic mastocytosis
  - Systemic mastocytosis with associated hematologic neoplasm
  - Aggressive systemic mastocytosis
  - Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytoma

What is mastocytosis?

• Clonal, neoplastic proliferation of mast cells
• Heterogeneous disorder:
  – Skin lesions that spontaneously regress to highly aggressive leukemias with short survival and multiorgan failure
• Subtypes determined by distribution and clinical manifestations
Telangiectasia macularis eruptiva perstans (TMEP)
Adults with cutaneous mastocytosis lesions
-Urticaria pigmentosa
-TMEP

Systemic mastocytosis
-most indolent
-fewer advanced

Cutaneous mastocytosis only
-sampling error

Work up:
1. Skin biopsy
2. Serum tryptase (basal and event-related)
3. Bone marrow biopsy with appropriate ancillary studies

Clinically Relevant Mediators Released from Mast Cells and Putative Effects.

**Cardiovascular**
- Hypotension
- Syncope or near syncope
- Light-headedness
- Tachycardia

**Cutaneous**
- Flushing
- Pruritus
- Urticaria
- Angioedema

**Digestive**
- Abdominal cramps
- Diarrhea
- Esophageal reflux
- Nausea and vomiting

**Musculoskeletal**
- Aches
- Bone pain
- Osteopenia
- Osteoporosis

**Respiratory**
- Nasal congestion
- Nasal pruritus
- Shortness of breath
- Throat swelling
- Wheezing

**Systemic**
- Fatigue
- Generalized malaise
- Weight loss

**Neurologic**
- Anxiety
- Depression
- Decreased concentration and memory
- Insomnia
- Migraines

**Mast-Cell Activators**
- Allergens,
- bacteria,
- cytokines,
- drugs,
- fungi,
- peptides,
- toxins,
- and viruses

**Mast cells**
- CRH, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase
- Histamine, interleukin-6, CysLTs, PAF, PGD₂
- CRH, histamine, interleukin-6, neurotensin, PAF, PGD₂, serotonin, TNF, tryptase, VIP
- Interleukin-6, PGD₂, RANKL, TNF, Tryptase

**Pathogenesis of SM**

- Somatic *KIT* point mutations in neoplastic mast cells
- Constitutive activation of the receptor tyrosine kinase *KIT*
- Induces increased mast cell proliferation and motility, resulting in infiltration of neoplastic mast cells into various organs

Classification of Mastocytosis

Cutaneous mastocytosis (CM)  Systemic mastocytosis (SM)
Classification of Mastocytosis

Systemic mastocytosis (SM)
- Indolent SM
- Smoldering SM
- SM with an associated hematologic neoplasm (SM-AHN)
- Aggressive SM
- Mast cell leukemia

Mast cell sarcoma
Classification of Mastocytosis

CM

More indolent SM
- Indolent SM
- Smoldering SM

“Advanced” SM
- SM with an associated hematologic neoplasm (SM-AHN)
- Aggressive SM
- Mast cell leukemia
- Mast cell sarcoma

Systemic mastocytosis (SM)
**Advanced Systemic Mastocytosis**

ASM (1+ “C”=cytoreductive requiring findings)

- **BM dysfunction → cytopenias**
- **Palpable hepatomegaly with impaired liver function, ascites, +/- portal hypertension**
- **Skeletal involvement → large osteolytic lesions, and/or pathological fractures**
- **Palpable splenomegaly w/ hypersplenism**
- **Malabsorption, weight loss due to GI mast cell infiltrates, hypoalbuminemia**

**Mast cell leukemia**

≥20% mast cells on aspirate/PB

**SM + AHN**

-met WHO criteria for an associated hematological neoplasm
-met SM criteria
Cytology of mast cells

Normal/reactive/well-differentiated

Atypical type I

Atypical type II

Metachromatic blast

Cytology of mast cells

Normal/reactive/well-differentiated

Atypical type I

Atypical type II

Metachromatic blast

Indolent systemic mastocytosis
ASM-AHN

ASM-MDS/MPN,U

ASM-CMML

tryptase

CD117
Mast cell leukemia

Bone marrow aspirate

Laboratory values:
Hb: 8.8 g/dL
WBC, PLT: Normal
Serum tryptase: 763

Blood smear
Bone marrow biopsy
Tryptase IHC positive
KIT D816V positive

MAST CELL ANALYSIS

CD117

CD2

CD25

CD25
Overall Survival

Kaplan–Meier survival for SM patients classified by WHO disease type compared with the expected age and sex-matched US population’s survival for the entire cohort.

Lim, KH. Blood. 2009 Jun 4;113(23):5727.
**KIT Mutations:**

**Implications for TK Inhibitors**

- **Juxtamembrane domain**
- **Transmembrane domain**
- **Extracellular ligand-binding domain**
- **Tyrosine kinase domain 1**
- **Tyrosine kinase domain 2**
- **Kinase insert**
- **Dimerization domain**

- **GIST: Gastrointestinal stromal tumors; SM: Systemic Mastocytosis; AML: acute myelogenous leukemia; NK/T-CL: Natural killer/T-cell lymphoma**

- **Imatinib sensitive**
- **Imatinib resistant**

- **Rare**

- **D816V~80%**

- **Rare**

- **GIST Exon 9**
  - **GIST: Gastrointestinal stromal tumors**
  - **Exon 9**

- **GIST Exon 11**
  - **Sinonasal NK/T-CL V559I, E561K**
  - **GIST Exon 13**
  - **SM D816V, Y; GIST Exon 17**
  - **AML: D816V, Y**
  - **Germ cell tumors: D816H**
  - **Sinonasal NK/T-CL D816N, D825A**

- **Imatinib sensitive**
- **Imatinib resistant**

- **GIST Exon 8**
  - **AML (Asp 419)**

- **SM V560G; GIST Exon 11**
Treatment

- Challenging due to the diversity and complexity of disease and the lack of a standard and highly effective therapy
- Current therapies include:
  - Observation
  - Topical therapies for cutaneous disease
  - Symptomatic noncytoreductive therapies
  - Cytoreductive therapy
    - Indicated by the presence of organ dysfunction
    - Used to reduce mast cell burden

Sensitivity of c-KIT D816V-Transformed Ba/F3 Cell Lines to Midostaurin and Imatinib

- Midostaurin inhibited growth of all c-KIT-transformed Ba/F3 cell lines.
- Cell lines resistant to imatinib due to expression of c-KIT D816V are inhibited by midostaurin.
- Results have been confirmed in additional cell lines.

IC\textsubscript{50} for midostaurin: 44 nM
IC\textsubscript{50} for imatinib: > 1 uM

Midostaurin

- Potent inhibitor of all common mutant forms of c-KIT, including D816V, D816Y
- May preferentially inhibit cells expressing mutant c-KIT compared to wild-type c-KIT
- Counteracts anti-IgE-induced release of histamine in blood basophils and cultured cord blood cell-derived mast cells
  - Effects were dose-dependent; occurred at pharmacologic concentrations

Activity of the tyrosine kinase inhibitor PKC412 in a patient with mast cell leukemia with the D816V KIT mutation

The majority of patients with systemic mast cell disease express the imatinib-resistant Asp816Val (D816V) mutation in the KIT receptor tyrosine kinase. Limited treatment options exist for aggressive systemic mastocytosis (ASM) and mast cell leukemia (MCL). We evaluated whether PKC412, a small-molecule inhibitor of KIT with a different chemical structure from imatinib, may have therapeutic use in advanced SM with the D816V KIT mutation. We treated a patient with MCL (with an associated myelodysplastic syndrome [MDS]) myeloproliferative disorder (MPD) based on in vitro studies demonstrating that PKC412 could inhibit D816V KIT-transformed Ba/F3 cell growth with a 50% inhibitory concentration (IC50) of 30 nM to 40 nM. The patient exhibited a partial response with significant resolution of liver function abnormalities. In addition, PKC412 treatment resulted in a significant decline in the percentage of peripheral blood mast cells and serum histamine levels and was associated with a decrease in KIT phosphorylation and D816V KIT mutant cell death and progression. Myeloid blast counts also decreased. This case is a feasible treatment option for patients with advanced SM with a KIT D816V mutation.
Efficacy and Safety of Midostaurin in Advanced Systemic Mastocytosis

Jason Gotlib, M.D., Hanneke C. Kluin-Nelemans, M.D., Ph.D.,
Tracy I. George, M.D., Cem Akin, M.D., Ph.D., Karl Sotlar, M.D.,
Olivier Hermine, M.D., Ph.D., Farrukh T. Awan, M.D., Elizabeth Hexner, M.D.,
Michael J. Mauro, M.D., David W. Sternberg, M.D., Ph.D.,
Matthieu Villeneuve, M.Sc., Alice Huntsman Labeled, Ph.D.,
Eric J. Stanek, Pharm.D., Karin Hartmann, M.D., Hans-Peter Horny, M.D.,
Peter Valent, M.D., and Andreas Reiter, M.D.
All patients/safety population (n = 116)

Unevaluable for response (n = 27)
- Absence of measurable C-findings (n = 14)
- Measurable C-findings considered unrelated to SM (n = 13)

Primary efficacy population (n = 89)
- ASM (n = 16)
- SM-AHN (n = 57)
- MCL (n = 16)

Discontinued (n = 19)
- Adverse events (n = 6; 2 suspected drug related)
- Progressive disease (n = 7)
- Withdrawn consent (n = 2)
- Death (n = 1)
- Protocol deviation (n = 1)
- Lost to follow-up (n = 1)
- Administrative problems (n = 1)

Completed study or ongoing (n = 24)

Discontinued (n = 65)
- Adverse events (n = 18; 11 suspected drug related)
- Progressive disease (n = 31)
- Withdrawn consent (n = 9)
- Death (n = 5)
- Protocol deviation (n = 1)
- Abnormal test results (n = 1)
## Baseline Patient and Disease Characteristics

<table>
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<th>Characteristic</th>
<th>Intention-to-Treat Population (N = 116)</th>
<th>Primary Efficacy Population (N = 89)</th>
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<td>Age — yr</td>
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<tr>
<td>Median</td>
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<td>64</td>
</tr>
<tr>
<td>Range</td>
<td>25–82</td>
<td>25–82</td>
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<tr>
<td>Male sex — no. (%)</td>
<td>76 (66)</td>
<td>57 (64)</td>
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<td>ECOG performance status — no. (%)†</td>
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<tr>
<td>0 or 1</td>
<td>77 (66)</td>
<td>57 (64)</td>
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<td>2 or 3</td>
<td>39 (34)</td>
<td>32 (36)</td>
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<td>No. of previous therapies — no. of patients (%)</td>
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<td>0</td>
<td>64 (55)</td>
<td>52 (58)</td>
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<td>1</td>
<td>29 (25)</td>
<td>21 (24)</td>
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<tr>
<td>2</td>
<td>15 (13)</td>
<td>12 (13)</td>
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<tr>
<td>≥3‡</td>
<td>8 (7)</td>
<td>4 (4)</td>
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<td>Subtype of advanced systemic mastocytosis — no. (%)</td>
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<td></td>
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<tr>
<td>Aggressive systemic mastocytosis</td>
<td>ND</td>
<td>16 (18)</td>
</tr>
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<td>Systemic mastocytosis with an AHN</td>
<td>ND</td>
<td>57 (64)</td>
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<tr>
<td>Mast-cell leukemia</td>
<td>21 (18)</td>
<td>16 (18)</td>
</tr>
<tr>
<td>KIT D816 mutation status — no. (%)</td>
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<td></td>
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<tr>
<td>Positive</td>
<td>98 (84)</td>
<td>77 (87)§</td>
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<tr>
<td>Negative</td>
<td>13 (11)</td>
<td>10 (11)</td>
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<tr>
<td>Unknown</td>
<td>5 (4)</td>
<td>2 (2)</td>
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<tr>
<td>Bone marrow mast-cell burden — %</td>
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<tr>
<td>Median</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Range</td>
<td>3–98</td>
<td>8–98</td>
</tr>
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<td>Serum tryptase level — µg/liter</td>
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<tr>
<td>Median</td>
<td>200</td>
<td>236</td>
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<td>Range</td>
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<td>No. of C-findings per patient — no. of patients (%)¶</td>
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<td>1</td>
<td>31 (27)</td>
<td>31 (35)</td>
</tr>
<tr>
<td>2</td>
<td>20 (17)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>≥3</td>
<td>38 (33)</td>
<td>38 (43)</td>
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</table>

* Data on additional baseline characteristics are provided in Table S6 in the Supplementary Appendix. AHN denotes associated hematologic neoplasm, and ND not determined.
† Values for the Eastern Cooperative Oncology Group (ECOG) performance status range from 0 to 5, with 0 indicating no symptoms and higher numbers indicating increasing tumor-associated disability.
‡ Some patients with SM-AHN, therapy was directed toward the associated hematologic neoplasm.
§ A total of 73 patients were positive for the KIT D816V mutation, 3 were positive for the KIT D816Y mutation, and 1 was positive for the KIT D816L mutation.
¶ Clinical findings that are related to organ damage from infiltrating mast cells are referred to as C-findings. Only measurable C-findings were eligible for this study; transfusion-independent and transfusion-dependent anemia and thrombocytopenia, neutropenia, liver-function abnormalities (increased levels of alanine aminotransferase, aspartate aminotransferase, or total bilirubin), hypoalbuminemia, and medically documented loss of at least 10% of body weight within 6 months before study entry.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Any Subtype of Advanced Systemic Mastocytosis (N=89)</th>
<th>Aggressive Systemic Mastocytosis (N=16)</th>
<th>Systemic Mastocytosis with an AHN (N=57)</th>
<th>Mast-Cell Leukemia (N=16)</th>
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<tr>
<td></td>
<td>major or partial response as best overall response</td>
<td>major or partial response as best overall response</td>
<td>major or partial response as best overall response</td>
<td>major or partial response as best overall response</td>
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<tr>
<td>patients with response — no.</td>
<td>53</td>
<td>12</td>
<td>33</td>
<td>8</td>
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<tr>
<td>overall response rate (95% CI) — %</td>
<td>60 (49–70)</td>
<td>75 (48–93)</td>
<td>58 (44–71)</td>
<td>50 (25–75)</td>
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<tr>
<td>duration of response — mo</td>
<td>median</td>
<td>24.1</td>
<td>NR</td>
<td>12.7</td>
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<td>95% CI</td>
<td>10.8–NE</td>
<td>24.1–NE</td>
<td>7.4–31.4</td>
<td>3.6–NE</td>
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<td>best overall response — no. (%)</td>
<td>major response</td>
<td>40 (45)</td>
<td>10 (62)</td>
<td>23 (40)</td>
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<tr>
<td>complete remission</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>incomplete remission</td>
<td>19 (21)</td>
<td>6 (38)</td>
<td>9 (16)</td>
<td>4 (25)</td>
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<tr>
<td>pure clinical response</td>
<td>15 (17)</td>
<td>4 (25)</td>
<td>9 (16)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>unspecified</td>
<td>6 (7)</td>
<td>0</td>
<td>5 (9)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>partial response</td>
<td>13 (15)</td>
<td>2 (12)</td>
<td>10 (18)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>good partial response</td>
<td>11 (12)</td>
<td>1 (6)</td>
<td>10 (18)</td>
<td>0</td>
</tr>
<tr>
<td>minor partial response</td>
<td>2 (2)</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>stable disease</td>
<td>11 (12)</td>
<td>1 (6)</td>
<td>7 (12)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>progressive disease</td>
<td>10 (11)</td>
<td>1 (6)</td>
<td>6 (11)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>patient could not be evaluated for response†</td>
<td>15 (17)</td>
<td>2 (12)</td>
<td>11 (19)</td>
<td>2 (12)</td>
</tr>
</tbody>
</table>
Overall Survival

A Overall Survival

Median Overall Survival (95% CI)

Intention-to-Treat Population: 33.9 (20.3–45.5)
Primary Efficacy Population: 28.7 (18.1–NE)

Kaplan–Meier Estimates of Overall Survival Rate (95% CI)

1 Yr 2 Yr 3 Yr

1 Yr: 76 (67–83) 72 (61–80)
2 Yr: 53 (43–62) 53 (41–63)
3 Yr: 46 (35–57) 46 (32–58)

No. at Risk

Intention-to-treat population: 116 113 105 102 91 87 83 80 70 61 54 44 38 36 28 25 24 20 19 15 13 11 10 5 3 2 0
Primary efficacy population: 89 87 80 77 66 62 59 56 48 43 38 30 26 24 17 15 15 12 12 8 7 5 5 4 2 2 0
Response over Time

- Major Response
- Partial Response
- Stable Disease
- Progressive Disease
- Not Evaluable

Patients (%)

<table>
<thead>
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<th>Months</th>
<th>Response over Time</th>
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<tr>
<td>2</td>
<td>13, 11, 17, 16, 21, 19, 10, 13, 13</td>
</tr>
<tr>
<td>3</td>
<td>19, 8, 9, 11, 12, 12, 10, 10, 13</td>
</tr>
<tr>
<td>4</td>
<td>16, 8, 4, 9, 11, 12, 10, 9, 4</td>
</tr>
<tr>
<td>5</td>
<td>20, 3, 3, 11, 10, 5, 8, 9, 4</td>
</tr>
<tr>
<td>6</td>
<td>13, 8, 3, 11, 10, 5, 8, 9, 4</td>
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<td>7</td>
<td>19, 3, 3, 11, 10, 5, 8, 9, 4</td>
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<td>9</td>
<td>12, 3, 3, 11, 10, 5, 8, 9, 4</td>
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<td>10</td>
<td>8, 3, 3, 11, 10, 5, 8, 9, 4</td>
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<td>11</td>
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<tr>
<td>12</td>
<td>11, 3, 3, 11, 10, 5, 8, 9, 4</td>
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n = 89, 85, 74, 70, 66, 61, 59, 55, 49, 48, 47, 46
## Overall Response Rate by Subgroups

<table>
<thead>
<tr>
<th>Category</th>
<th>Response (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 89)</td>
<td>60 (49-70)</td>
</tr>
<tr>
<td>ASM (n = 16)</td>
<td>75 (48-93)</td>
</tr>
<tr>
<td>SM-AHN (n = 57)</td>
<td>58 (44-71)</td>
</tr>
<tr>
<td>MCL (n = 16)</td>
<td>50 (25-75)</td>
</tr>
<tr>
<td>MCL (n = 16)</td>
<td>50 (25-75)</td>
</tr>
<tr>
<td>Non-MCL (n = 73)*</td>
<td>62 (50-73)</td>
</tr>
<tr>
<td>With AHN (n = 63)</td>
<td>57 (44-70)</td>
</tr>
<tr>
<td>Without AHN (n = 26)</td>
<td>73 (45-92)</td>
</tr>
<tr>
<td><strong>KIT D816V+ (n = 73)</strong></td>
<td>63 (51-74)</td>
</tr>
<tr>
<td><strong>KIT D816V-/unknown (n = 16)</strong></td>
<td>44 (20-70)</td>
</tr>
<tr>
<td>Prior therapies (n = 37)</td>
<td>62 (45-78)</td>
</tr>
<tr>
<td>No prior therapies (n = 52)</td>
<td>58 (43-71)</td>
</tr>
</tbody>
</table>
Overall Survival by Response in Mast Cell Leukemia

<table>
<thead>
<tr>
<th></th>
<th>Median OS (95% CI, months)</th>
<th>1-Year OS</th>
<th>2-Year OS</th>
<th>3-Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders (n = 8)</td>
<td>NR (9.4-NE)</td>
<td>86 (33-98)</td>
<td>57 (8-89)</td>
<td>57 (8-89)</td>
</tr>
<tr>
<td>Nonresponders (n = 8)</td>
<td>7.6 (3.4-8.7)</td>
<td>13 (1-42)</td>
<td>0 (NE-NE)</td>
<td>0 (NE-NE)</td>
</tr>
</tbody>
</table>

HR = 0.049 (95% CI, 0.006-0.414)  
P = 0.0056
Clinicopathological Measures of Response

- Bone marrow mast cell burden
- Serum tryptase
- Spleen volume

Histologic Regression in ASM patient
Improvements in Alkaline Phosphatase, Eosinophil, and Monocyte Levels

- **Alk Phos**
- **Eos**
- **Monos**
Improvements in Quality of Life
Study Conclusions

- **Midostaurin can:**
  - Reverse organ damage
  - Decrease splenomegaly
  - Decrease BM mast cells
  - Improve patient-reported symptoms and quality of life
Midostaurin in advanced SM, 10 year follow-up

a) Bone marrow mast cell burden

Best % change in bone marrow mast cell burden from baseline

Clinical Responders (n=17)
Clinical Nonresponders (n=8)

Best % change in bone marrow mast cell burden:
Median -60% (range -100 to 200%)

---

b) Serum tryptase level

Best % change in serum tryptase level from baseline

Clinical Responders (n=18)
Clinical Nonresponders (n=8)

Best % change in serum tryptase level:
Median -47% (range -99 to 54%)

---

*a* N=25 instead of 26. One responder did not have quantification of bone marrow mast cells at baseline; described as 'focally involved'.

*b* Responder with best value of 0% change in bone marrow mast cells vs baseline
Midostaurin treatment is associated with a significant decrease in CD25 expression on neoplastic mast cells by flow cytometry in patients #1, #2, and #3 before (A-C) and on day 28 (patient #1, D), day 89 (patient #2, E), and day 336 (patient #3, F) of midostaurin therapy.
Midostaurin therapy is associated with sustained decreases in CD25 expression on neoplastic mast cells by mean fluorescence intensity (MFI; A, C, E) and percent of mast cells positive for CD25 (B, D, F) over time in patient #1 (A-B), patient #2 (C-D), and patient #3 (E-F). The shaded area indicates time on midostaurin therapy.
Proposed mechanism for midostaurin-induced CD25 downregulation

Changes in the intracellular localization of STAT5 with midostaurin
Outline

• Updates on classification
• Advanced mastocytosis
• A case report
• Clinical trials
• Other potential therapies
CD30 expression in systemic mastocytosis

CD30 expression in systemic mastocytosis

Clinical trial with anti-CD30 drug does not demonstrate clinical activity in advanced systemic mastocytosis

10 patients:
- 8 stable disease
- 1 progressive disease
- 1 not evaluable due to early death unrelated to study

Immunohistochemistry

Smoldering systemic mastocytosis

Mast cell leukemia

M Geeze, E Hatch, C Martin, S Perkins, K Hartmann, P Valent, J Gotlib, D Lidke. USCAP 2016
Flow cytometry

Indolent SM

Mast cell leukemia

Indolent SM

Mast cell leukemia

Indolent SM

Aggressive SM
Multiplex immunohistofluorescence

Mast cell leukemia, spleen

Tryptase (red), PDL1 (green)
Cutaneous mastocytosis

Mast cell leukemia, spleen

Tryptase (red)
PDL1 (green)

A

B

C

Overlay

Cutaneous mastocytosis
**PD-1/PD-L1 are novel therapeutic targets for mastocytosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PD-L1 expression</th>
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</tr>
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<tbody>
<tr>
<td>SM</td>
<td>17/22 (77%)</td>
<td>0/25</td>
</tr>
<tr>
<td>CM</td>
<td>23/25 (92%)</td>
<td>4/27 (15%)</td>
</tr>
<tr>
<td>MML</td>
<td>1/2</td>
<td>0/2</td>
</tr>
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<td>MMAS</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>MPN</td>
<td>0/16</td>
<td>0/17</td>
</tr>
<tr>
<td>MDS</td>
<td>0/18</td>
<td>0/18</td>
</tr>
<tr>
<td>MDS/MPN</td>
<td>0/5</td>
<td>0/5</td>
</tr>
<tr>
<td>Healthy/reactive BM</td>
<td>0/15</td>
<td>0/21</td>
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PD-1/PD-L1 are novel therapeutic targets for mastocytosis

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<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>MCL</td>
<td>3/3 (100%)</td>
</tr>
<tr>
<td>ASM</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>SM-AHN</td>
<td>9/12 (75%)</td>
</tr>
<tr>
<td>SSM</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>ISM</td>
<td>3/4 (75%)</td>
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Conclusions

• Updates on classification
• Advanced mastocytosis
• A case report
• Clinical trials
• Other potential therapies
Thank you collaborators!

Jason Gotlib
Dan Arber
Susan Atwater
Bruno Medeiros
Athena Cherry

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Ilana Kepten
Jeffrey Tyner

Natasha Savage
Farrukh Awan

Peter Valent

Timothy Graubert

Dan DeAngelo

Eric Hsi

Hans-Peter Horny
Karl Sotlar

REMA (Spanish Network on Mastocytosis)