Exploring the Spectrum of Indolent Systemic Mastocytosis: Analysis of High-Risk Disease Features in the PIONEER Study

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American Academy of Allergy Asthma & Immunology (AAAAI) Annual Meeting, Washington, DC; February 23–26, 2024
Indolent Systemic Mastocytosis: A KIT D816V-Driven Disease with Substantial Impact on Quality of Life

• Systemic mastocytosis (SM) is driven by aberrant mast cells carrying a KIT D816V mutation in >95% of cases1,2

• Indolent systemic mastocytosis (ISM) is the most common subtype of SM and, over time, patients can progress to advanced disease in 5-18% of cases3-5

• Clinical manifestations of ISM are caused by the aberrant KIT D816V-mutant mast cells and most commonly include cutaneous, gastrointestinal, and neurocognitive symptoms, which may be debilitating6-8

ISM, indolent systemic mastocytosis; SM, systemic mastocytosis.
The PIONEER Trial Examined Avapritinib, a KIT D816V Inhibitor, as a Treatment for ISM\textsuperscript{1,2}

PIioneer is a randomized placebo-controlled clinical trial studying avapritinib, a KIT D816V-selective inhibitor, for the treatment of ISM.

**Part 1**
- Determination of Recommended Part 2 dose
- \(N=212\)
- R 2:1

**Part 2**
- Double-blind treatment period
- (24 weeks)
- Avapritinib 25 mg QD
- \(n=141\)
- Placebo
- \(n=71\)
- Both groups continued optimized BSC as needed

**Part 3**
- Open-label extension
- (5 years)
- All Part 1 and 2 patients on avapritinib (ongoing)

**Goal 1:** Assess efficacy and safety of avapritinib for the treatment of ISM

- Avapritinib met all primary and key secondary endpoints with high statistical significance and is now approved for adult patients with ISM.
The PIONEER Trial Examined Avapritinib, a KIT D816V Inhibitor, as a Treatment for ISM\textsuperscript{1,2}

PIioneer is a randomized placebo-controlled clinical trial studying avapritinib, a KIT D816V-specific inhibitor, for the treatment of ISM.

Goal 1: Assess efficacy and safety of avapritinib for the treatment of ISM

\checkmark Avapritinib met all primary and key secondary endpoints with high statistical significance and is now approved for adult patients with ISM.

Goal 2: Leverage the large, well-characterized cohort of patients enrolled in the PIONEER trial to learn more about the ISM disease spectrum.

BSC, best supportive care; ISM, indolent systemic mastocytosis; QD, once daily; R, randomized.

The Cohort of Patients Enrolled in the PIONEER Trial Represents a Novel Opportunity to Better Understand ISM

Individual patient assessments performed both at baseline and throughout the PIONEER trial

**SYMPTOMS**
- Total symptom score as determined by the ISM-SAF tool, designed and validated specifically for patients with ISM

**BIOMARKERS**
- Bone marrow mast cells
- Skin biopsy of lesional and non-lesional skin
  - Tryptase
- KIT D816V variant allele frequency (VAF) in the peripheral blood

**PHYSICAL FINDINGS**
- Splenomegaly
- Hepatomegaly

ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; VAF, variant allele frequency.
Patients Enrolled in the PIONEER Trial Have a High Symptom Burden and a Wide Range of Mast Cell Burden

<table>
<thead>
<tr>
<th>Patient demographic</th>
<th>Patients in the PIONEER trial (n=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>49.7 (18–79)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>179 (72.8)</td>
</tr>
<tr>
<td>Baseline BMI (kg/m²), median (range)</td>
<td>28.2 (17.6–51.4)</td>
</tr>
<tr>
<td>Medical History of Anaphylaxis, n (%)</td>
<td>40 (16.3)</td>
</tr>
</tbody>
</table>

**ISM symptom burden**

| TSS score, mean (SD)a | 48.5 (19.6) |

**Mast cell burden**

| Median serum tryptase (central), ng/mL (range) | 40.3 (3.6–590.4) |
| Median bone marrow biopsy mast-cells (central), % (range) | 7.0 (1.0–60.0) |
| Median KIT D816V VAF in peripheral blood, % (range) | 0.35 (undetectableb–41.29) |

**Physical exam findings**

| Palpable spleen, n (%) | 4 (1.7) |
| Palpable liver, n (%) | 7 (2.9) |

aPIONEER enrolled patients with moderate to severe ISM based on TSS score; bLimit of detection of assay ≥0.02% BMI, bone marrow index; SD, standard deviation; TSS, Total Symptom Score.
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- Tryptase
- **KIT D816V VAF in the peripheral blood**

**PHYSICAL FINDINGS**
- Splenomegaly
- Hepatomegaly

**Why focus on KIT D816V VAF in the peripheral blood?**

- It is an easily assessed biomarker that represents a novel tool for physicians in the clinic
- There is growing importance within the SM field (elevated KIT D816V VAF in the peripheral blood is newly recognized as a “B finding” in WHO 2022 criteria)
- KIT D816V VAF in the peripheral blood measures an aspect of ISM that is unique – it measures “multilineage involvement” of the KIT mutation and may be prognostic

ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; SM, systemic mastocytosis; WHO, World Health Organization.

KIT D816V VAF in the Peripheral Blood Indicates Where in the Hematopoietic Lineage the D816V Mutation Occurs
**KIT** D816V VAF in the Peripheral Blood Indicates Where in the Hematopoietic Lineage the D816V Mutation Occurs

**KIT** D816V mutation restricted to mast cell

**KIT** D816V VAF level in peripheral blood

Low **KIT** D816V VAF in the peripheral blood

**KIT** D816V Mutation

Diagram showing the hematopoietic lineage with arrows indicating the flow from Hematopoietic Stem Cell to Common Myeloid Progenitor, and then to Monocyte, Neutrophil, Eosinophil, Tissue-Resident Mast Cell, and **KIT** D816V Mutation.
**KIT D816V VAF in the Peripheral Blood Indicates Where in the Hematopoietic Lineage the D816V Mutation Occurs**

*KIT D816V mutation in early progenitor cell*

**High KIT D816V VAF in the peripheral blood**
A *KIT* D816V VAF in the Peripheral Blood of 6% is Highly Specific for Multilineage Involvement of the *KIT* D816V Mutation

**KIT** D816V VAF level in peripheral blood

- **6%** *KIT* D816V VAF cutoff:
  - 98% specific and 32% sensitive for multilineage involvement of the *KIT* mutation

- **6%** *KIT* D816V VAF cutoff:
  - The median VAF of treatment naïve patients who enrolled on the PATHFINDER trial of avapritinib in advanced SM

- **15% (37/246)** of patients on PIONEER had a *KIT* D816V VAF of ≥6%

- **85% (209/246)** of patients on PIONEER had a *KIT* D816V VAF of <6%

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Regardless of VAF, Patients in the PIONEER Trial Had High Symptom Burden and Poor Scores On Quality-of-Life Metrics at Baseline

<table>
<thead>
<tr>
<th>Baseline QoL or Symptom Burden Measurement at Time of Enrollment in PIONEER</th>
<th>PIONEER Patients with KIT D816V VAF &lt;6% (n=209)</th>
<th>PIONEER Patients with KIT D816V VAF ≥6% (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median <strong>Total Symptom Score</strong> on ISM-SAF (110 point scale, higher = more severe)</td>
<td>45.2</td>
<td>47.7</td>
</tr>
<tr>
<td>Median <strong>Mastocytosis QoL Score</strong> (100 point scale, higher = greater impact on QoL)</td>
<td>55.6</td>
<td>57.4</td>
</tr>
<tr>
<td>Median Score on <strong>EQ-5D-5L Visual Analog Scale</strong> (100 point scale, higher = more severe)</td>
<td>57.0</td>
<td>55.0</td>
</tr>
<tr>
<td>Median <strong>Patient Global Impression of Severity</strong> (5 point scale, higher = more severe)</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Median <strong>SF-12 Physical Component Score</strong> (100 point scale, lower = greater impact on QoL)</td>
<td>34.3</td>
<td>35.3</td>
</tr>
<tr>
<td>Median <strong>SF-12 Mental Component Score</strong> (100 point scale, lower = greater impact on QoL)</td>
<td>42.0</td>
<td>38.8</td>
</tr>
</tbody>
</table>

ED-SD-5L, EuroQol-5 Dimensions-5 Level; QoL, quality of life; SF-12, 12-item short form.
At Baseline, Patients with ISM and High *KIT* D816V VAF in the Peripheral Blood Had Characteristics Approaching Advanced Disease

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>PIONEER Patients with <em>KIT</em> D816V VAF &lt;6% (n=209)</th>
<th>PIONEER Patients with <em>KIT</em> D816V VAF ≥6% (n=37)</th>
</tr>
</thead>
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<tr>
<td>Median (range) Age (years)</td>
<td>50.0 (21–79)</td>
<td>56.0 (18–77)</td>
</tr>
<tr>
<td>Median (range) BMI (kg/m²)</td>
<td>28.5 (17.6–51.4)</td>
<td>26.4 (19.2–38.6)</td>
</tr>
<tr>
<td>Median (range) time to diagnosis (months)</td>
<td>58.7</td>
<td>100.5</td>
</tr>
<tr>
<td>Medical history positive for anaphylaxis (n, %)</td>
<td>38 (18.2)</td>
<td>2 (5.4)</td>
</tr>
</tbody>
</table>

AdvSM, advanced systemic mastocytosis.
ISM Patients With High \( KIT \) D816V VAF in the Peripheral Blood Had Findings Associated With Higher Burden/More Advanced Disease at Baseline

<table>
<thead>
<tr>
<th>Baseline disease burden</th>
<th>PIONEER Patients with ( KIT ) D816V VAF &lt;6% (n=209)</th>
<th>PIONEER Patients with ( KIT ) D816V VAF ≥6% (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) serum tryptase (ng/mL)</td>
<td>36 (4–288.0)</td>
<td>119 (11–590.4)</td>
</tr>
<tr>
<td>Median (range) ( KIT ) D816V VAF (%)</td>
<td>0.2 (undetectable(^a)–5.5)</td>
<td>14.9 (6.3%–41.3)</td>
</tr>
<tr>
<td>Median (range) bone marrow mast cell burden in core biopsy (%)</td>
<td>5 (1–50)</td>
<td>20 (1–60)</td>
</tr>
<tr>
<td>Rates of palpable livers (n, %)</td>
<td>3 (1.4)(^b)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Rates of palpable spleens (n, %)</td>
<td>1 (0.5)(^c)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Median (range) mast cell density in skin lesions (cells/mm(^2))</td>
<td>400 (53–4300)</td>
<td>761 (100–2870)</td>
</tr>
</tbody>
</table>

\(^a\)Limit of detection of assay ≥0.02\%, \(^b\)n=208, \(^c\)n=205.
ISM Patients With High $KIT$ D816V VAF in the Peripheral Blood Had Findings Associated With Organ Involvement/More Advanced Disease at Baseline

<table>
<thead>
<tr>
<th>Marker of Organ Involvement</th>
<th>PIONEER Patients with $KIT$ D816V VAF &lt;6% (n=209)</th>
<th>PIONEER Patients with $KIT$ D816V VAF ≥6% (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) alkaline phosphatase (IU/L)</td>
<td>76.0 (35–229)</td>
<td>93.0 (45–186)</td>
</tr>
<tr>
<td>Number of patients with at least one pathogenic mutation in $SRSF2$, $ASXL1$, $RUNX1$, or $DNMT3A$ (n, %)</td>
<td>12 (5.7)</td>
<td>5 (13.5)</td>
</tr>
</tbody>
</table>
High *KIT* D816V VAF Patients With ISM Are More Likely to Have Shortened Overall Survival per IPSM Prognostic Score

**International Prognostic Scoring System**

- Risk factors:
  - Alkaline phosphatase ≥100 U/L
  - Age ≥60 years

**Historical data**

<table>
<thead>
<tr>
<th>IPSM Risk Group for Shortened OS</th>
<th>Patients with <em>KIT</em> D816V VAF &lt;6% (n=209)</th>
<th>Patients with <em>KIT</em> D816V VAF ≥6% (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Risk Factors</td>
<td>135 (65%)</td>
<td>15 (41%)</td>
</tr>
<tr>
<td>≥1 Risk Factors</td>
<td>74 (35%)</td>
<td>22 (59%)</td>
</tr>
</tbody>
</table>

AdvSM, advanced systemic mastocytosis; IPSM, International Prognostic Scoring System; OS, overall survival.

High \( KIT \) D816V VAF Patients With ISM Are More Likely to Have Shortened Overall Survival per GPSM-OS Prognostic Score

Global Prognostic Score for Systemic Mastocytosis\(^1\)

- Risk factors:
  - Hemoglobin ≤110 g/dL
  - Alkaline Phosphatase ≥140 IU/L
  - At least one mutation in SRSF2, ASXL1, RUNX1, or DNMT3A

<table>
<thead>
<tr>
<th>Baseline Data from PIONEER</th>
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<tbody>
<tr>
<td>GPSM Risk Group for Shortened OS</td>
</tr>
<tr>
<td>0 risk factors</td>
</tr>
<tr>
<td>1–2 risk factors</td>
</tr>
<tr>
<td>All 3 risk factors</td>
</tr>
</tbody>
</table>

**Historical data\(^1\)**

GPSM-OS, global prognostic score for systemic mastocytosis.

**KIT D816V VAF in the Peripheral Blood at Baseline Helps to Define Where a Patient May Lie on the Spectrum of ISM**

Lower **KIT D816V VAF**
- 85% of patients in PIONEER

Younger
- Shorter history of disease
- Lower risk of progression to AdvSM
- Lower impact on overall survival
  - Lower tryptase
- Lower bone marrow mast cells
- Higher rates of anaphylaxis

**High symptom burden and decreased QoL**

ISM

**KIT D816V VAF of 6%**

Higher **KIT D816V VAF**
- 15% of patients in PIONEER

Older
- Longer history of disease
- Higher risk of progression to AdvSM
- Higher impact on overall survival
  - Higher tryptase
- Higher bone marrow mast cells
- Lower rates of anaphylaxis

BMM, bone marrow mastocytosis.
Conclusions

- ISM is a disease driven by *KIT*D816V-mutant mast cells that can be targeted by avapritinib

- *KIT*D816V VAF in the peripheral blood can be used to identify patients with multilineage involvement of the KIT mutation

- Patients with ISM and a high *KIT*D816V VAF in the peripheral blood accounted for 15% of the PIONEER study population at baseline, and were found to have more aggressive disease features with an overall phenotype approaching that of advanced disease

- Patients with ISM can have debilitating symptoms and low quality of life, regardless of *KIT*D816V VAF

- Further research is needed to understand the relationship between peripheral blood *KIT*D816V VAF and the natural history of ISM

ISM, Indolent systemic mastocytosis; VAF, variant allele frequency.
Acknowledgements

• We thank the patients and their families for making the PIONEER study possible
• We also thank the investigators and clinical trial teams who participated in the study
• Medical writing support was provided by Akanksha Srivastava, MSc, and Travis Taylor, BA, of Paragon (a division of Prime, Knutsford, UK). Funded by Blueprint Medicines Corporation. The sponsor reviewed and provided feedback on the presentation. However, the authors had full editorial control and provided final approval of all content
Disclosures

• Dr Maurer has received honoraria (advisory board, speaker) and/or institutional grant/research support from Allakos, Amgen, AstraZeneca, Bayer, Blueprint Medicines Corporation, Celldex, Dr. Pfleger, FAES, Genentech, GI Innovation, GSK, Innate Pharma, Kyowa Kirin, Lilly, Merckle Recordati, Moxie, Novartis, Regeneron, Roche, Sanofi, Third Harmonic Bio, UCB, and Uriach.