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

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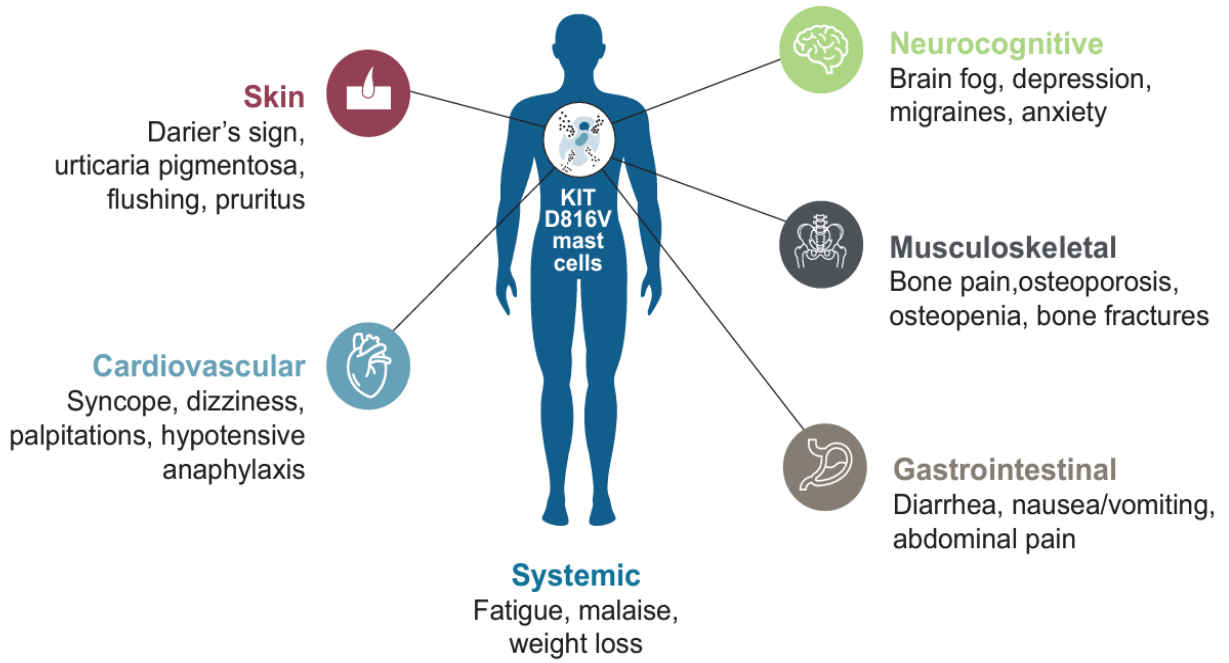
Indolent systemic mastocytosis: A *KIT* D816V-driven disease with substantial impact on quality of life

- Systemic mastocytosis (SM) is driven by aberrant mast cells carrying a *KIT* D816V mutation in >95% of cases[1,2]
- Indolent systemic mastocytosis (ISM) is the most common subtype of SM and, over time, patients can progress to advanced disease in 5-18% of cases[3-5]
- 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 debilitating[6–8]

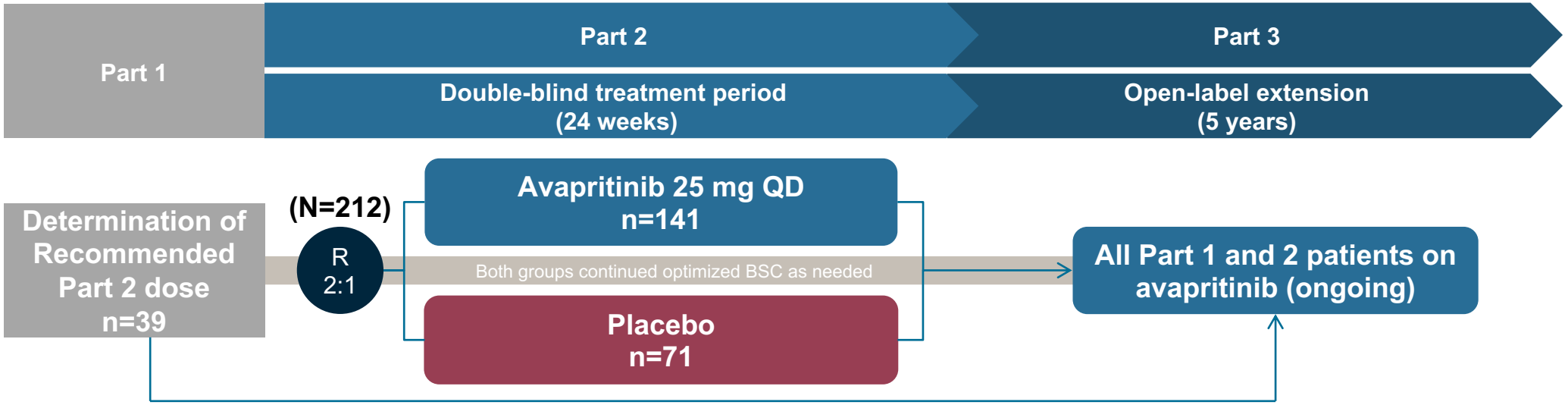


ISM, indolent systemic mastocytosis; SM, systemic mastocytosis.

1. Kristensen T et al. *J Mol Diagn.* 2011;13:180–188; 2. Cohen SS et al. *Br J Haematol.* 2014;166:521–528; 3. Mukherjee S et al. Presented at ASH 2022. Poster #3053; 4. Escribano L et al. *J Allergy Clin Immunol.* 2009;124(3):514–521; 5. Trizuljak J et al. *Allergy* 2020;75(8):1927–1938; 6. Mesa RA et al. *Cancer.* 2022;128:3691–3699; 7. van Anrooij B. et al. *Allergy.* 2016;71:1585–1593; 8. Hartmann K et al. *J Allergy Clin Immunol.* 2016;137:35–45.

The PIONEER trial examined avapritinib, a KIT D816V inhibitor, as a treatment for ISM[1,2]

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



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**

BSC, best supportive care; ISM, indolent systemic masyocytosis; QD, once daily; R, randomized.
1. Castells et al. Presented at *AAAAI* 2023. 2. Gotlib et al. *NEJM Evidence* 2023;2(6):EVIDoa2200339.

The PIONEER trial examined avapritinib, a KIT D816V inhibitor, as a treatment for ISM[1,2]

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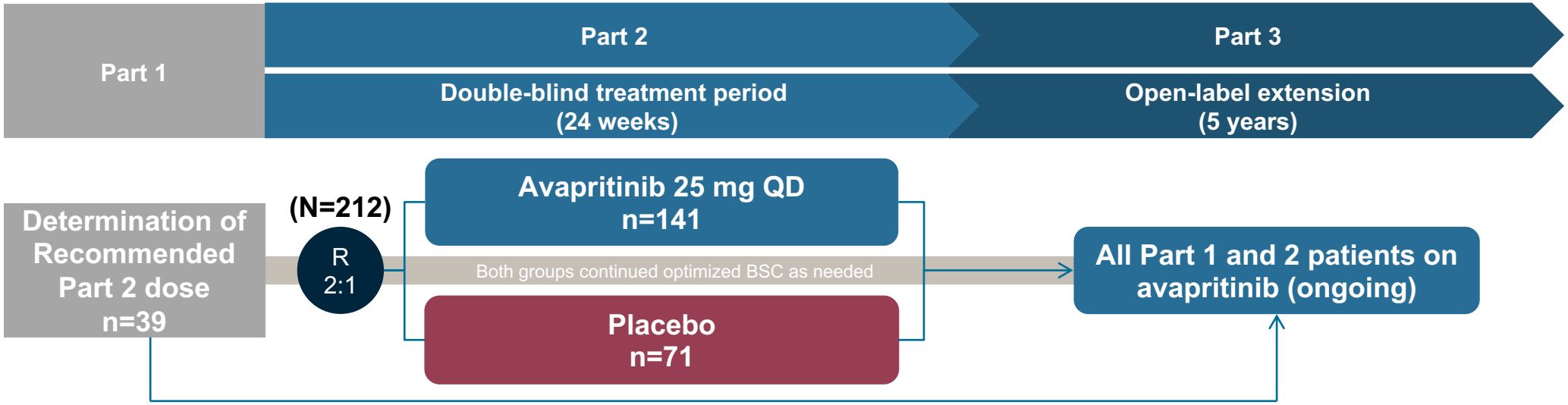

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Goal 2: Leverage the **large, well-characterized cohort of patients enrolled in the PIONEER trial** to learn more about the ISM disease spectrum

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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 masyocytosis; 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

Patient demographic	Patients in the PIONEER trial (n=246)
Age (years), median (range)	49.7 (18–79)
Female, n (%)	179 (72.8)
Baseline BMI (kg/m^2), median (range)	28.2 (17.6–51.4)
Medical History of Anaphylaxis, n (%)	40 (16.3)
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 (undetectable[b]–41.29)
Physical exam findings	
Palpable spleen, n (%)	4 (1.7)
Palpable liver, n (%)	7 (2.9)

[a]PIONEER enrolled patients with moderate to severe ISM based on TSS score; [b]Limit of detection of assay ≥0.02%
BMI, bone marrow index; SD, standard deviation; TSS, Total Symptom Score..

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BIOMARKERS
- Bone marrow mast cells
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- ***KIT* D816V VAF in the peripheral blood**

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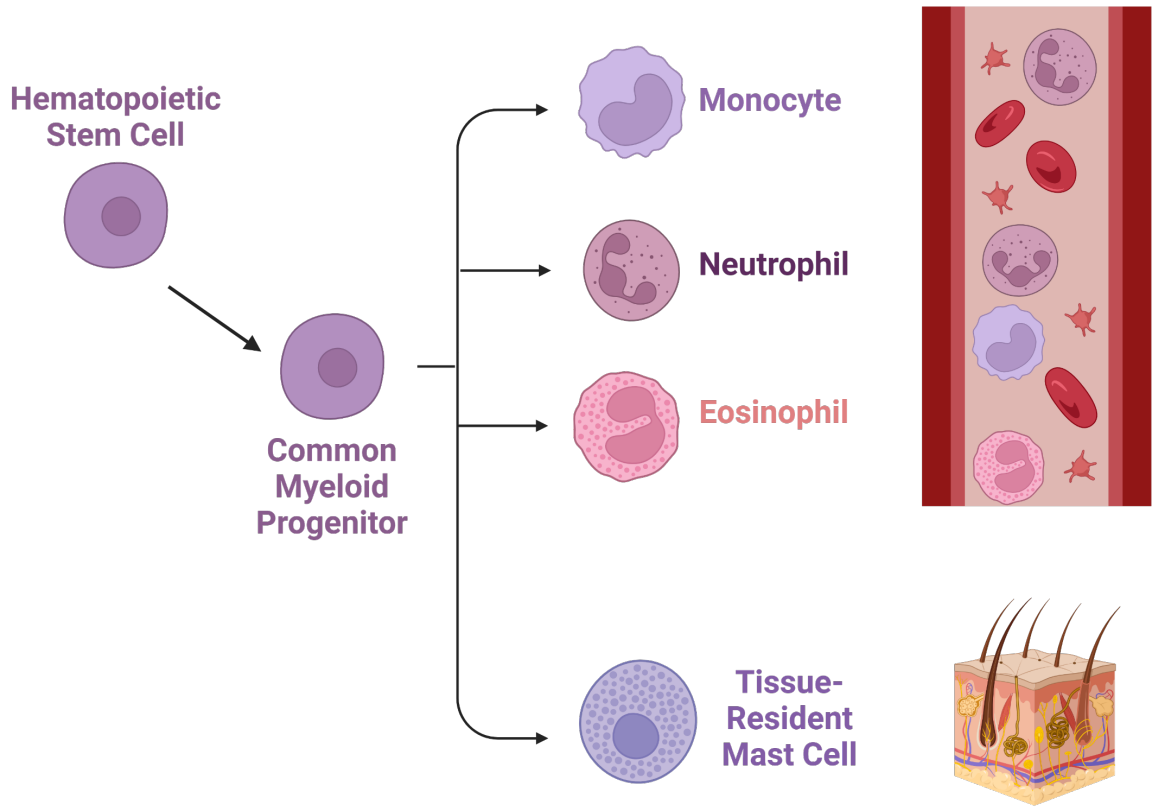
Why focus on *KIT* D816V VAF in the peripheral blood?

- 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)[1]
- *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[2]

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

1. Khoury et al. *Leukemia* 2022;36:1703–1719. 2. Muñoz-González *Blood* 2019;134(5):456-468.

KIT D816V VAF in the peripheral blood indicates where in the hematopoietic lineage the D816V mutation occurs



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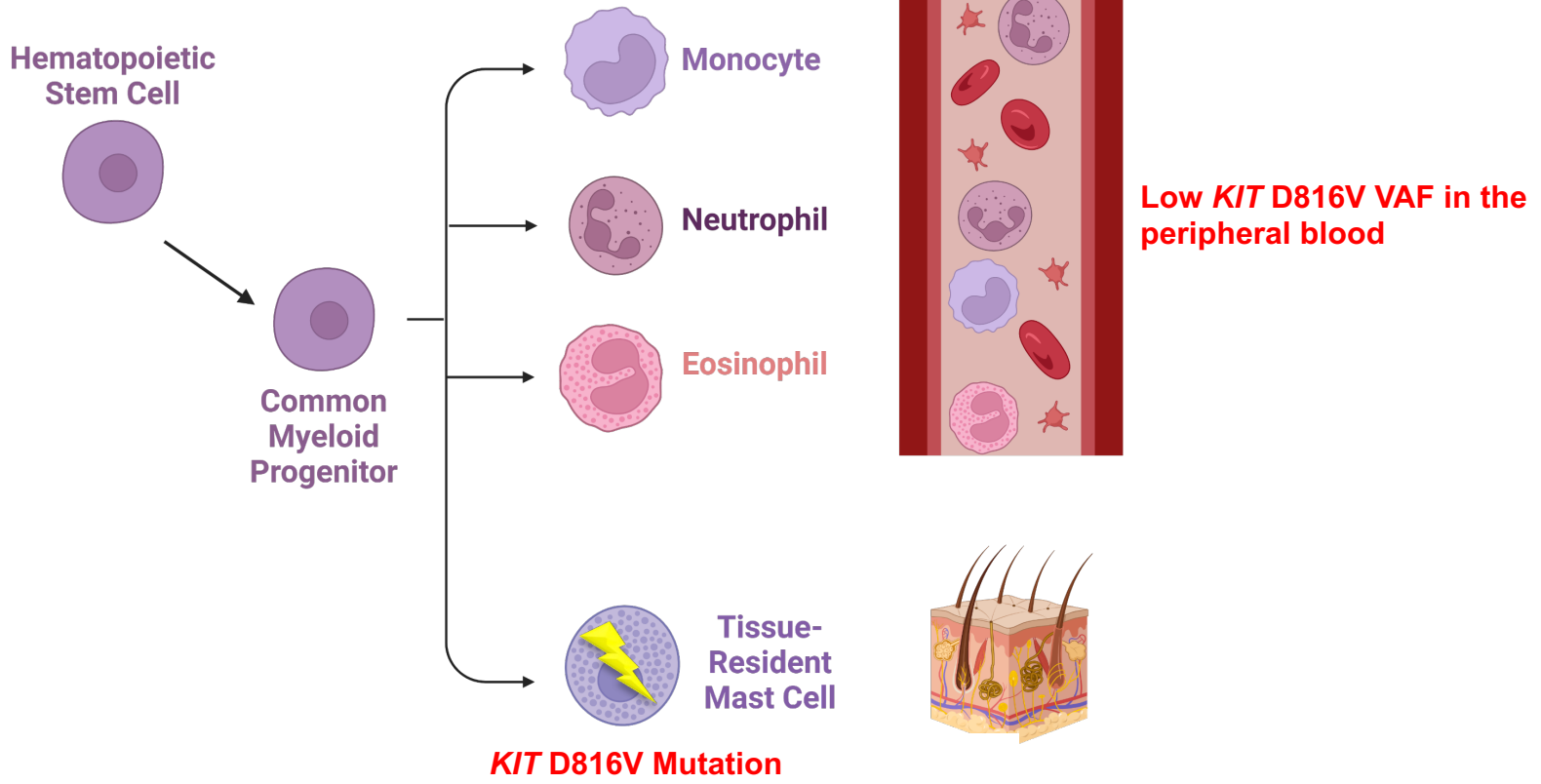
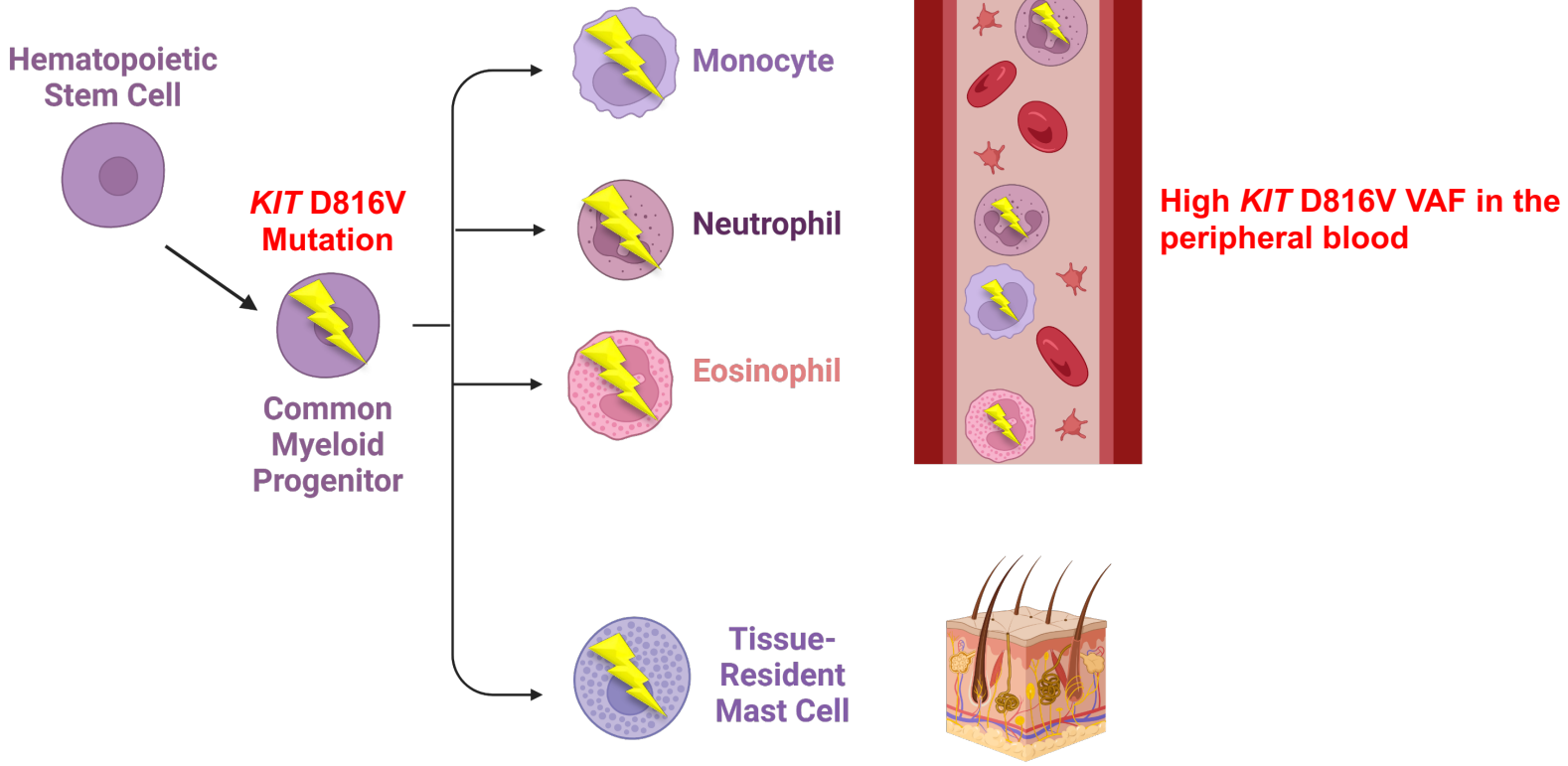
KIT D816V mutation restricted to mast cell



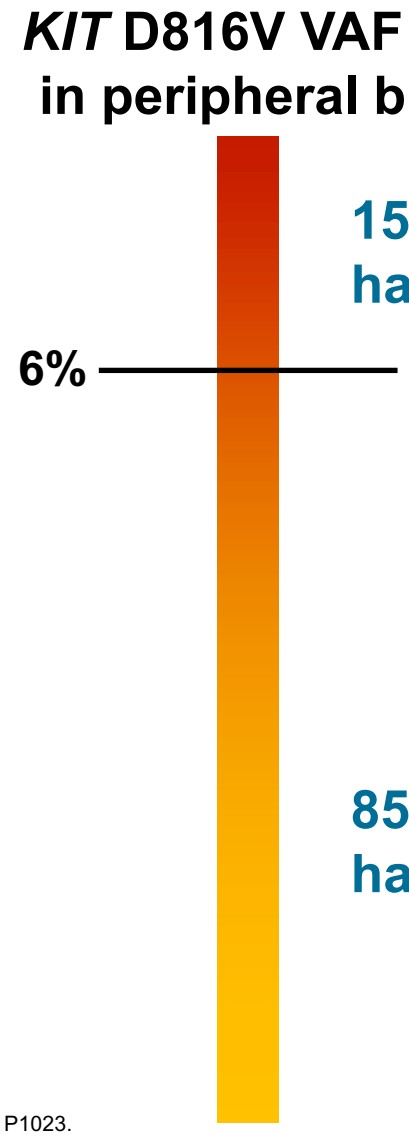
KIT D816V VAF level in peripheral blood

KIT D816V VAF in the peripheral blood indicates where in the hematopoietic lineage the D816V mutation occurs

KIT D816V mutation in early progenitor cell



A *KIT* D816V VAF in the peripheral blood of 6% is highly specific for multilineage involvement of the *KIT* D816V mutation



6% *KIT* D816V VAF cutoff:
98% specific and 32% sensitive for multilineage involvement of the *KIT* mutation[1]

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

6% *KIT* D816V VAF cutoff:
The median VAF of treatment naïve patients who enrolled on the PATHFINDER trial of avapritinib in advanced SM[2]

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

1. Muñoz-González *Blood* 2019;134(5):456-468. 2. Gotlib et al. Presented at *EHA* 2023 Abstract P1023.

Regardless of VAF, patients in the PIONEER trial had high symptom burden and poor scores on quality-of-life metrics at baseline

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

ED-5D-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

Demographic Characteristic	PIONEER Patients with *KIT* D816V VAF <6% (n=209)	PIONEER Patients with *KIT* D816V VAF ≥6% (n=37)
Median (range) Age (years)	50.0 (21–79)	56.0 (18–77)
Median (range) BMI (kg/m^2)	28.5 (17.6–51.4)	26.4 (19.2–38.6)
Median (range) time to diagnosis (months)	58.7	100.5
Medical history positive for anaphylaxis (n, %)	38 (18.2)	2 (5.4)

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

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

[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

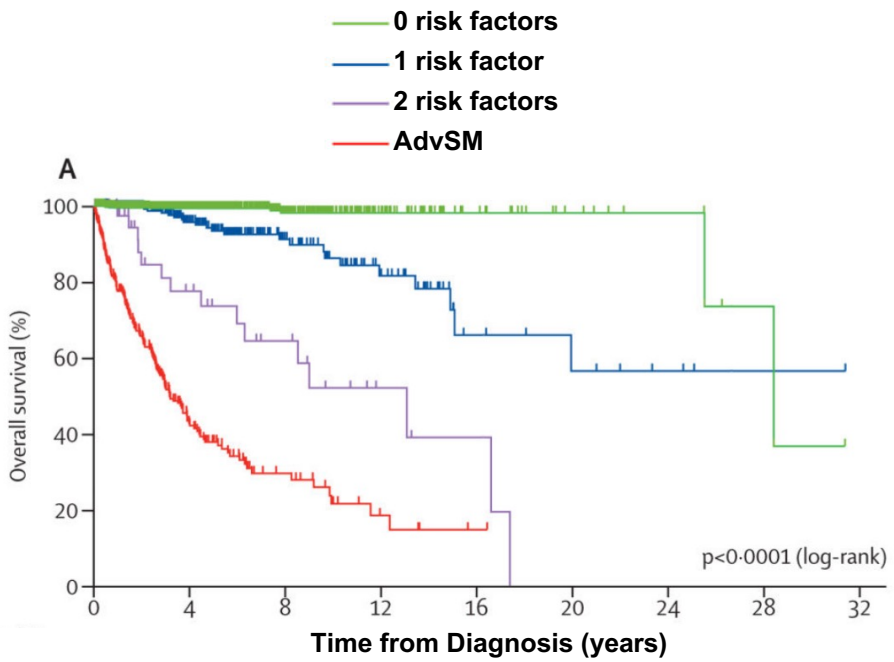
Marker of Organ Involvement	PIONEER Patients with *KIT* D816V VAF <6% (n=209)	PIONEER Patients with *KIT* D816V VAF ≥6% (n=37)
Median (range) alkaline phosphatase (IU/L)	76.0 (35–229)	93.0 (45–186)
Number of patients with at least one pathogenic mutation in *SRSF2*, *ASXL1*, *RUNX1*, or *DNMT3A* (n, %)	12 (5.7)	5 (13.5)

High *KIT* D816V VAF patients with ISM are more likely to have shortened overall survival per IPSM prognostic score

International Prognostic Scoring System[1]

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

Historical data[1]



Baseline Data from PIONEER

IPSM Risk Group for Shortened OS	Patients with *KIT* D816V VAF <6% (n=209)	Patients with *KIT* D816V VAF ≥6% (n=37)
0 Risk Factors	135 (65%)	15 (41%)
≥1 Risk Factors	74 (35%)	22 (59%)

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

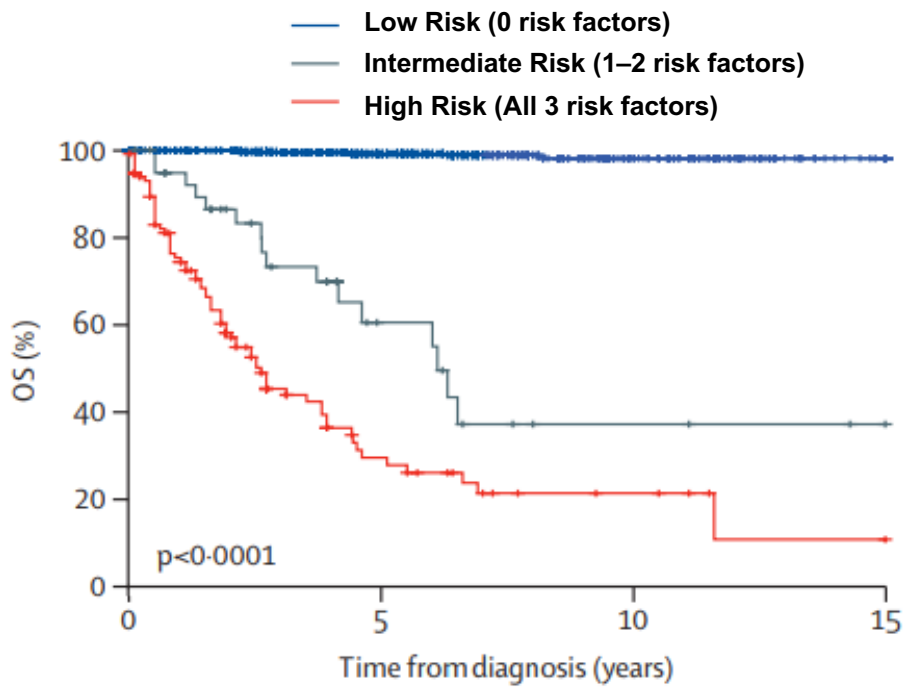
1. Sperr WR et al. *Lancet Haematol*. 2019;6(12):e638-e649.

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

Historical data[1]



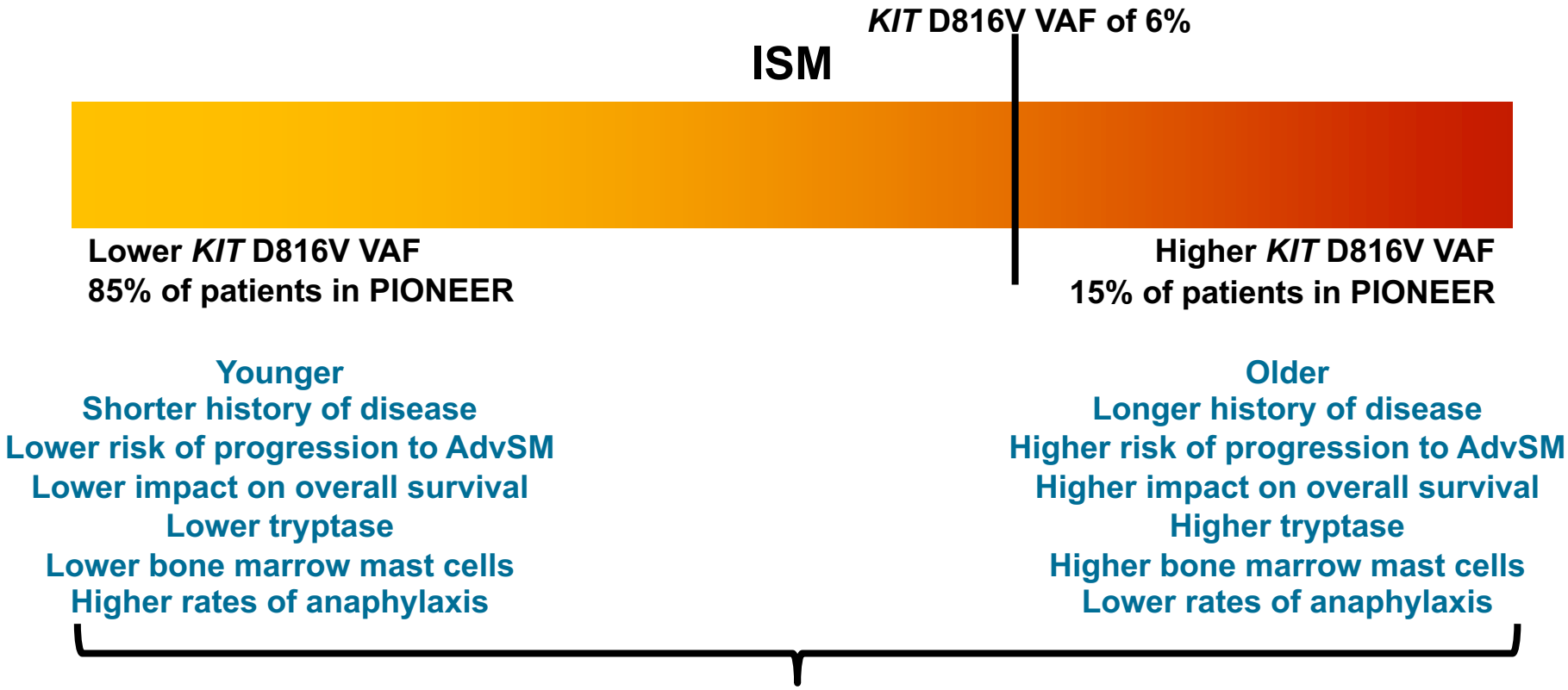
Baseline Data from PIONEER

GPSM Risk Group for Shortened OS	Patients with *KIT* D816V VAF <6% (n=209)	Patients with *KIT* D816V VAF ≥6% (n=37)
0 risk factors	185 (89%)	25 (68%)
1–2 risk factors	24 (11%)	10 (27%)
All 3 risk factors	0 (0%)	2 (5%)

GPSM-OS, global prognostic score for systemic mastocytosis.

1. Munoz-Gonzalez JI et al. *Lancet Haematol*. 2021; 8(3):e194-e204.

KIT D816V VAF in the peripheral blood at baseline helps to define where a patient may lie on the spectrum of ISM



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.

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