HIGH-RISK DISEASE FEATURES OF INDOLENT SYSTEMIC MASTOCYTOSIS AND METHODS FOR TREATING

RELATED APPLICATIONS

[001] This application claims the benefit of U.S. Provisional Application No. 63/549,930, filed on February 5, 2024, and U.S. Provisional Application No. 63/557,229, filed on February 23, 2024, the entire teachings of which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[002] Indolent systemic mastocytosis (ISM) includes patients with a wide range of mast cell (MC) disease burden and variable natural history of disease. ISM is a disease driven by KIT D816V-mutant mast cells that can be targeted by KIT D816V inhibitors e.g., avapritinib.

SUMMARY OF THE INVENTION

[003] Described herein are the results of an analysis of disease burden and prognostic tools that predict overall survival (OS) in patients with ISM enrolled in the PIONEER (NCT03731260) placebo-controlled trial of avapritinib. Characteristics associated with poor outcomes in patients with ISM enrolled in PIONEER, including risk for shortened OS, were identified in ~4–16% of patients. It has been discovered that KIT D816V Variant Allele Frequency (VAF) ≥6% in peripheral blood (PB) is associated with high-risk disease features of ISM. Patients with high-risk ISM have higher disease burden at baseline and may be at an increased risk of developing advanced disease. Thus, there is a need to treat patients with high-risk ISM. The administration of higher doses (i.e., amounts) of KIT D816V inhibitors to patients in need thereof has been found to effectively treat high risk ISM. Specifically, the administration of a dose of 50-100 mg QD of avapritinib to a patient in need thereof effectively treats high risk ISM.

DESCRIPTION OF THE FIGURE

[004] Figure 1 is a schematic which shows the design of the PIONEER trial which examined avapritinib for the treatment of ISM.

DETAILED DESCRIPTION

[005] The disclosure provides methods of identifying and treating patients with high risk indolent systemic mastocytosis.

[006] [Embodiment 1] A method of treating a patient with high risk indolent systemic mastocytosis (ISM) with a KIT D816V inhibitor, comprising:

(a) obtaining a blood sample from the patient;

(b) determining whether the patient with ISM has a D816V mutation in KIT having a variant allele frequency (VAF) ≥6% in peripheral blood; and

(c) administering a therapeutically effective amount of a KIT D816V inhibitor to the patient, if the patient is determined to have a KIT D816V VAF ≥6%.

[007] [Embodiment 2] The method of embodiment 1, wherein the VAF is measured by a method selected from the group consisting of Quantitative real-time PCR (Q-PCR), Digital PCR (d-PCR) including droplet digital PCR (ddPCR), Next generation sequencing (NGS), Duplex Sequencing (Duplex-Seq) and Super-RCA.

[008] [Embodiment 2a] The method of embodiment 1, wherein the VAF is measured by a method selected from the group consisting of Quantitative real-time PCR (Q-PCR), Digital PCR (d-PCR) including droplet digital PCR (ddPCR), Next generation sequencing (NGS), Duplex Sequencing (Duplex-Seq), Super-RCA, and allele-specific oligonucleotide PCR (ASO-PCR).

[009] [Embodiment 3] The method of embodiment 1 or 2 or 2a, wherein the KIT D816V inhibitor is avapritinib.

[0010] [Embodiment 4] A method of determining whether a patient has high risk indolent mastocytosis (ISM), comprising:

(a) obtaining a biological sample from the patient;

(b) determining whether the patient has a D816V mutation in KIT having a variant allele frequency (VAF) ≥6% in peripheral blood;

(c) identifying the patient as having high risk ISM, if the patient has a KIT D816V VAF ≥6%.

[0011] [Embodiment 5] The method of embodiment 4, wherein the biological sample is peripheral blood.

[0012] [Embodiment 6] The method of embodiment 4 or 5, wherein the VAF is measured by a method selected from the group consisting of Quantitative real-time PCR (Q-PCR),

Digital PCR (d-PCR) including droplet digital PCR (ddPCR), Next generation sequencing (NGS), Duplex Sequencing (Duplex-Seq) NS and Super-RCA.

[0013] [Embodiment 6a] The method of embodiment 4 or 5, wherein the VAF is measured by a method selected from the group consisting of Quantitative real-time PCR (Q-PCR), Digital PCR (d-PCR) including droplet digital PCR (ddPCR), Next generation sequencing (NGS), Duplex Sequencing (Duplex-Seq) Super-RCA, and allele-specific oligonucleotide PCR (ASO-PCR).

[0014] [Embodiment 7] The method of any one of embodiments 4-6 or 6a, wherein the patient is identified as having high risk ISM and administered a therapeutically effective amount of a KIT D816V inhibitor.

[0015] [Embodiment 8] The method of any one of embodiments 4, 5, 6, 6a or 7, wherein the therapeutically effective amount of the KIT D816V inhibitor is a higher amount.

[0016] [Embodiment 9] The method of any one of embodiments 4-6, 6a, 7, or 8, wherein the higher amount is an amount of the KIT D816V inhibitor that is above the amount administered to treat a patient with ISM that is not high-risk ISM.

[0017] [Embodiment 10] The method of any one of embodiments 4-6, 6a, or 7-9, wherein the KIT D816V inhibitor is avapritinib.

[0018] [Embodiment 11] The method of embodiment 10, wherein the amount of avapritinib is 50-100 mg QD.

[0019] [Embodiment 12] The method embodiment 11, wherein the amount of avapritinib is 50 mg QD.

[0020] [Embodiment 13] The method of embodiment 12, wherein the amount of avapritinib is 100 mg QD.

[0021] ISM is a KIT D816V-driven disease with a substantial impact on quality of life. Systemic mastocytosis (SM) is a spectrum of diseases driven by aberrant mast cells carrying a KIT D816V mutation in >95% of cases. ISM is the most common subtype of SM and can progress to higher disease burden in up to 5-18% of cases (Mukherjee S et al., Ash 2022. Poster #3053; Escribano L et al J. Allergy Clin Immunol. 2009; 124(3):514-521; Trizuljak J et al. Allergy 2020; 75(8): 1927-1938). 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 (Mesa RA et al. Cancer. 2022; 128: 3691-3699; van Anrooij B. et al Allergy 2016;71: 1585-1593; Hartmann K et al. J Allergy Clin Immunol. 2016; 137:35-45).

[0022] PIONEER is a randomized placebo-controlled clinical trial studying avapritinib, a selective KIT D816V inhibitor, as a treatment for ISM. The PIONEER trial assessed the efficacy and safety of avapritinib for the treatment of ISM. Avapritinib met all primary and key secondary endpoints with high statistical significance and was approved by the FDA in May 2023 for the treatment of adult patients with ISM at the recommended approved dosage of 25 mg avapritinib orally once daily. Patients enrolled in the PIONEER trial have moderate-to-severe symptom burden and a wide range of mast cell burden. Further analysis of patients enrolled in the PIONEER trial has resulted in the identification of a subset of ISM patients who have high risk ISM at baseline (Table 1).

Table 1.

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)
Physician 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

[b] Limit of detection of assay $\geq$0.02%

[0023] Individual patient assessments with respect to symptoms, biomarkers, and physical findings were performed at baseline and throughout the PIONEER trial. The total symptom score was determined using the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF), a tool designed and validated specifically for patients with ISM. Physical findings included splenomegaly and hepatomegaly, and biomarker analysis included bone marrow mast cells, skin biopsy of lesional and non-lesional skin, tryptase, and KIT D816V VAF in PB.

[0024] KIT D816V VAF in PB is a biomarker that can be easily assessed by physicians. Within the SM field, KIT D816V VAF in the PB is recognized as a "B" finding in WHO

2022 criteria (Khoury Leukemia 2022;36:1703-1719). The WHO 2022 criteria related to KIT VAF is a KIT D816V VAF in PB of ≥10%. KIT D816V VAF is an aspect of ISM that is unique from tryptase. It measures "multilineage involvement" of the KIT mutation and may be prognostic (Munoz-Gonzalez, Blood 2019; 134(5): 456-468).

[0025] KIT D816V VAF in the PB indicates where in the hematopoietic lineage the D816V mutation occurs. When the KIT D816V mutation in PB is found to be restricted to a tissue-resident mast call, this is characteristic of a patient having a low KIT D816V VAF level. In contrast, when the KIT D816V mutation in PB is found in an early progenitor cell e.g., a hematopoietic stem cell, this is characteristic of a patient with a high KIT D816V VAF level. A KIT D816V VAF in the PB of 6% is highly specific for multilineage involvement of the KIT D816V mutation.

[0026] The PIONEER clinical trial enrolled 251 patients with ISM with moderate-to-severe symptoms. Two independent, validated prognostics tools, the Global Prognostic Score for Overall Survival in Systemic Mastocytosis (GPSM-OS) and the International Prognostic Scoring system for Mastocytosis (IPSM), were used to identify patients at higher risk for shortened OS and the scores of patients on these tools were compared between the low versus high PB KIT D816V VAF groups. Baseline evaluations, including serum tryptase level, bone marrow (BM) MC burden, hepatomegaly (palpable liver), and skin lesion MC burden, were also compared in patients with low versus high PB KIT D816V VAF.

[0027] Table 2 shows baseline quality of life (QoL) or symptom burden measurement at time of enrollment in PIONEER. Of the patients on the PIONEER trial, at baseline, 15% (37/246) were found to have a KIT D816V VAF of ≥6% and 85% (209/246) of patients in PIONEER had a KIT D816V VAF of <6%. Regardless of VAF, patients with ISM have high symptom burden and poor scores on quality-of-life metrics at baseline.

Table 2.

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

[0028] As shown in Table 3 below, at baseline ISM patients with high KIT D816V VAF in the PB have characteristics approaching advanced disease.

Table 3.

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)

[0029] ISM patients with high KIT D816V VAF in PB have findings that are associated with higher burden / more advanced disease at baseline (Table 4).

Table 4.

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

[0030] ISM patients with high KIT D816V VAF in PB have findings associated with organ involvement/more advanced disease at baseline (Table 5).

Table 5.

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, AXSL1, RUNX1, or DNMT3A* (n, %)	12 (5.7)	5 (13.5)

[0031] Patients with KIT D816V VAF ≥6% (15% of the PIONEER study population) were predicted to have higher risk for shortened OS per International Prognostic Scoring System (IPSM) (Sperr WR et al. Lancet Haematol. 2019;6(12):e638-e649). Risk factors of the IPSM include: alkaline phosphatase ≥100 U/L and age ≥60 years. Baseline Data from PIONEER are shown in the following Table 6:

Table 6.

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

[0032] Patients with KIT D816V VAF ≥6% were predicted to have higher risk for shortened OS per global prognostic score for systemic mastocytosis (GPSM)-OS prognostic score (Munos-Gonzalez Jl et al. Lancet Haematol. 2021; 8(3):e194-e204). Risk factors of the GPSM-OS are hemoglobin ≤11.0 g/dL, alkaline phosphatase ≥140 IU/L, and at least one mutation in SRSF2, ASXL1, RUNX1, or DNMT3A. Baseline Data from PIONEER is shown in the following Table 7:

Table 7.

GP SM Risk Group for Shortened OS	**PIONEER Patients with *KIT* D816V VAF <6% (n=209)**	**PIONEER 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%)

[0033] Patients with KIT D816V VAF ≥6% had greater baseline disease burden, indicated by elevated median (range) serum tryptase (119 ng/mL [11–590] versus 36 ng/mL

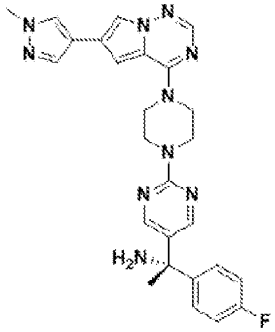
[4–288]), median (range) BM MC burden (20% [1–60] versus 5% [1–50]), rates of hepatomegaly (11% versus 1%) and median (range) skin lesion MC density (761 counts/mm^2 [100–2870] versus 400 counts/mm2 [53–4300]).

[0034] KIT D816V VAF in the PB can be used to identify patients with multilineage involvement of the KIT mutation. KIT D816V VAF in the PB at baseline helps to define where a patient may lie on the spectrum of ISM. ISM patients with high KIT D816V VAF in PB accounted for 15% of the PIONEER study population and were found to have more aggressive disease features and an overall phenotype approaching that of advanced SM. ISM patients have debilitating symptoms and low quality of life (QoL) regardless of KIT D816V VAF. Quantitative KIT D816V VAF testing in patients with ISM can help to identify patients with high-risk disease.

[0035] ISM patients with high-risk disease (KIT D816V VAF $\geq$6%) may be treated with a KIT D816V inhibitor at a higher dose (amount). In some embodiments, the KIT D816V inhibitor is avapritinib. In some embodiments, the ISM patient with high-risk disease is treated with a therapeutically effective amount. In some embodiments, the amount is 50-100 mg QD avapritinib. In some embodiments, the amount is 50 mg QD avapritinib. In some embodiments, the amount is 100 mg QD avapritinib. In some embodiments, the amount of avapritinib administered to ISM patients with high-risk disease achieves durable improvements overall total symptom score. In some embodiments, the amount of avapritinib administered achieves durable improvements in one or more symptom domain scores. In some embodiments, the amount of avapritinib administered achieves durable improvements in quality of life measures. A durable improvement is a sustained and lasting positive change in a patient's condition that persists for a period of time. In one embodiment, a durable improvement lasts for a period of at least 96 weeks, at least 3 years, at least 4 years, at least 5 years. In one embodiment, a durable improvement provides long term benefit to the patient. Treatment of high-risk ISM patients with a KIT D816V inhibitor at a higher amount results in an improvement in treatment e.g., objective measures of mast cell burden such as a decrease in serum tryptase, a decrease in bone marrow mast cell numbers, a decrease in skin mast cell infiltrates, and a decrease in KIT D816V VAF in peripheral blood. In some embodiments, the treatment of high-risk ISM patients with a higher amount of KIT D816V inhibitor results in an improvement in symptoms e.g., TSS score, a reduction in episodes of anaphylaxis, and/or an improvement in bone health.

Definitions:

[0036] As used herein, "avapritinib" refers to a compound having the chemical name (S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine. The structure of avapritinib is:



Avapritinib was developed to selectively target KIT D816V and other KIT exon 17 mutations. Avapritinib is currently sold in the United States as the active pharmaceutical ingredient in AYVAKIT®. The recommended FDA approved dosage of avapritinib for ISM is 25 mg orally once daily. The preparation, solid forms and additional methods for treating patients with avapritinib are described in WO2015/057873, WO2020/210669, and US2024/0382493.

[0037] The term "KIT D816V inhibitor" refers to a compound or a pharmaceutically acceptable salt thereof that inhibits D816V mutant KIT protein kinase. Examples of KIT D816V inhibitors are avapritinib, elenestinib, and bezuclastinib.

[0038] As used herein, "a therapeutically effective amount" of a compound disclosed herein refers to an amount of the compound that will elicit a biological or medical response in a patient, *e.g.*, reduce or inhibit enzyme or protein activity, ameliorate symptoms, alleviate conditions, or slow or delay disease progression. In some aspects, a therapeutically effective amount of avapritinib is 25, 50 or 100 mg administered once a day. In some aspects, a therapeutically effective amount is safe and well-tolerated. In some aspects, a therapeutically effective amount achieves durable improvements in overall symptom score.

[0039] As used herein, the term "inhibit," "inhibition," or "inhibiting" refers to the reduction or suppression of a given disease, or a significant decrease in the baseline activity of a biological activity or process.

[0040] As used herein, the term "treat," "treating," or "treatment," when used in connection with a disease includes any effect, *e.g.*, lessening, reducing, modulating,

ameliorating, and/or eliminating, that results in the improvement of the disease. Improvements in or lessening the severity of any symptom of the disease can be readily assessed according to standard methods and techniques known in the art.

[0041] In some embodiments, treatment of the disease comprises a reduction of mast cell burden. In some embodiments, objective measures of mast cell burden include serum tryptase, bone marrow mast cell numbers, skin mast cell infiltrates, and KIT D816V VAF in blood.

[0042] In some embodiments, treatment comprises a reduction of systemic mastocytosis symptoms. Systemic mastocytosis symptoms include, but are not limited to, pruritus, flushing, GI cramping, diarrhea, anaphylaxis (especially to bee venom), bone pain, osteoporosis, and urticarial pigmentosa. In some embodiments, an ISM-SAF patient reported outcome (PRO) instrument is used to assess symptom improvement. The ISM-SAF PRO instrument is a questionnaire to specifically to assess symptoms in patients with ISM. In some embodiments, the ISM-SAF instrument is a 12-item patient reported outcome tool designed to assess symptoms in patients with ISM. Eleven items are graded on an 11-point scale (0 to 10, none to maximum severity), and 1 item (diarrhea) also assesses frequency. The ISM-SAF generates scores for each item, for the domains of skin, GI, pain and nonspecific symptoms, and a total symptom score (TSS).

[0043] In some embodiments, treatment comprises a reduction in episodes of anaphylaxis. In some embodiments, an "episode of anaphylaxis" is an episode of anaphylaxis treated with epinephrine. In some embodiments, treatment improves quality of life (QoL) as measured by one or more questionnaires. Non-limiting examples of QoL questionnaires include the MC-QoL, the PGIS, the SF-12, the PGIC, and the EQ-5D-EL. The MC-QoL is a disease-specific QoL tool developed specifically for use in patients with ISM and CM (Siebenhaar, F. et al., Allergy 71(6):869-77 (2016)). The MC-QoL contains 27 items assessing four domains: symptoms, emotions, social life/functioning, and skin. Items are assessed on a 5-point scale with a recall period of two weeks. The PGIS is a single-item scale that assesses a patient's perception of disease symptoms at a point in time. The PGIS has been widely used to evaluate a patient's overall sense of whether a treatment has been beneficial. The SF-12 was developed for the Medical Outcomes Study, a multiyear study of patients with chronic conditions. The instrument was designed to reduce respondent burden, while achieving minimum standards of precision for purposes of group comparisons involving multiple health dimensions. The questionnaire measures health and wellbeing using 8 health domains from the patient's perspective. The recall period is four weeks. The PGIC is

a single-item scale that assesses a patient's perception of change in disease symptoms at a point in time. The EQ-5D-5L is a standardized instrument for measuring generic health status. It is made up of two components: health state description and evaluation. Health status is measured in terms of five dimensions (5D): mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. Respondents self-rate their level of severity for each dimension using a 5-point scale. The recall period is "today" (Whynes, D.K., *Health Qual Life Outcome*s 6:94 (2008)).

[0044] In some embodiments, treatment comprises an improvement in bone density. Bone density is measured by a dual-energy x-ray absorptiometry scan assessing both lumbar spine and hip. In some embodiments, treatment does not affect bone density.

[0045] As used here, "PB" means peripheral blood.

[0046] As used herein "OS" means overall survival.

[0047] As used herein, "VAF" means Variant Allele Frequency.

[0048] As used herein, the term PIONEER refers to the placebo controlled trial of avapribinib (NCT03731260)(Gotlib NEJM, 2023;2(6))

Example 1: PIONEER Trial

[0049] The PIONEER trial examined avapritinib as a treatment for ISM (Figure 1). Patients whose ISM symptoms were uncontrolled (total symptom score [TSS] of ≥28 at screening), despite optimized best supportive care (BSC) with two or more antimediator drugs, were randomly assigned two to one to receive avapritinib 25 mg orally once daily plus BSC (henceforth termed avapritinib) or placebo plus BSC (henceforth termed placebo) for 24 weeks (also defined as cycle [C] 7 day [D]1; patients received avapritinib or placebo once daily for 4 weeks in each cycle). After completing 24 weeks of treatment with avapritinib or placebo, all patients were eligible to receive avapritinib 25 mg once daily for up to 5 years (Part 3). Randomization was stratified by serum tryptase level at screening (<20 ng/ml [capped at approximately 20% of enrolled patients] vs. ≥20 ng/ml). Part 3 is an open-label extension of PIONEER, which allows for characterization of longer-term experience with avapritinib. Part 3 includes an option for dose escalation to 50 mg once daily.

[0050] The primary endpoint of the trial is the mean change in ISM-SAF Total Symptom Score, from baseline to C7D1. Secondary endpoints include: Proportion of patients with a ≥ 50% reduction in serum tryptase from baseline to C7D1. Proportion of patients with a ≥ 50% reduction in peripheral blood KIT D816V allele fraction from baseline to C7D1 or undetectable (< 0.02%) for patients with detectable mutation at baseline. Proportion of patients with ≥ 50% reduction in ISM-SAF TSS from baseline to C7D1. Proportion of

patients with ≥ 30% reduction in ISM-SAF TSS from baseline to C7D1. Proportion of patients with a ≥ 50% reduction in bone marrow MCs from baseline to C7D1 or no aggregates for patients with aggregates at baseline.

Target Population / Main entry criteria:

1. Patients who are ≥ 18 years of age.
2. Patient must have SM, confirmed by Central Pathology Review of BM biopsy, and central review of B- and C-findings by WHO diagnostic criteria.
3. Patient must have moderate-to-severe symptoms based on minimum mean TSS over the 14-day eligibility screening period for assessment of TSS. Minimum TSS for eligibility is ≥ 28.
4. Patient must have failed to achieve adequate symptom control for 1 or more baseline symptoms, as determined by the Investigator, with at least 2 of the following symptomatic therapies administered: H1 blockers, H2 blockers, proton-pump inhibitors, leukotriene inhibitors, cromolyn sodium, corticosteroids, or omalizumab.
5. The patient's SM symptomatic therapies (e.g., H1 and H2 blockers) must be stable (same dose, no new medications ≥ 14 days before beginning the 14-day eligibility screening period for the assessment of ISM-SAF).
6. If the patient is receiving corticosteroids, the dose must be ≤ 20 mg/day prednisone or equivalent, and the dose must be stable for ≥ 14 days before beginning the 14-day eligibility screening period for assessment of ISM-SAF.
7. Patient must have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 to 2.
8. Patient must not have received prior treatment with avapritinib.
9. Patient must not have had any cytoreductive therapy including but not limited to masitinib and midostaurin, or investigational agent for < 14 days or 5 half-lives of the drug (whichever is longer), and for cladribine, interferon alpha, pegylated interferon, or antibody therapy < 28 days or 5 half-lives of the drug (whichever is longer), before beginning the 14-day eligibility screening period for assessment of ISM-SAF.
10. Patient must not have received radiotherapy or psoralen and ultraviolet A (PUVA) therapy < 14 days before beginning the 14-day eligibility screening period for assessment of ISM-SAF.
11. Patient must not have received any hematopoietic growth factor the preceding 14 days before beginning the 14-day eligibility screening period for assessment of ISM-SAF.

12. Patient must not require therapy with a concomitant medication that is a strong inhibitor, strong inducer, or moderate inducer of cytochrome P450 3A4 (CYP3A4).

13. Patient must not have a QT interval corrected using Fridericia's formula (QTcF) of > 480 msec.

14. Patient must not have a history of a seizure disorder (e.g., epilepsy) or requires antiseizure medication.

15. Patient must not have a history of a cerebrovascular accident or transient ischemic attacks within 12 months before the first dose of study drug.

16. Patient must not have a known risk or recent history (12 months before the first dose of study drug) of intracranial bleeding (ICB) (eg, brain aneurysm).

17. Patient must be able to give written informed consent.

Details on screening and baseline TSS determination and BSC medications.

Screening

[0051] After ISM-SAF symptom eligibility was confirmed through a 14-day average of TSS (screening TSS), the assessment and central review period began, which may have lasted up to 8 weeks.

[0052] Baseline TSS was calculated as the 14-day average of TSS prior to first dose date (i.e., cycle 1 day −14 to cycle 1 day −1). The TSS at 24 weeks (C7D1) was the 14-day average prior to C7D1 (i.e., day 155 to day 168). If a patient was missing more than 7 days of TSS within a 14-day period, the 14-day average TSS was considered as missing for the patient.

[0053] BSCs included the following classes of agents that block the action of histamine at H1 and H2 receptors; proton pump inhibitors; osteoclast inhibitors (such as bisphosphonates, denosumab); leukotriene receptor antagonists and synthesis inhibitors; corticosteroids; cromolyn sodium and other mast-cell stabilizers such as ketotifen; and the anti-immunoglobulin E (IgE) antibody therapy, omalizumab.

[0054] QoL was assessed at each study visit to Week 24 using the 12-Item Short-Form Health Survey (SF-12®),1 Mastocytosis Quality of Life Questionnaire (MC-QoL),2 European Quality of Life 5 Dimensions (EQ-5D-5L®). 3 QoL data were collected using an electronic tablet; however, in extenuating circumstances, were collected via paper form previously approved by the Institutional Review Board/ Independent Ethics Committee. The SF-12® questionnaire assessed functional health and well-being over the past week. The instrument was designed to reduce patient burden, while achieving minimum standards of precision for purposes of group comparisons involving multiple health dimensions. The

questionnaire measured health and well-being using eight health domains (physical functioning, physical role, body pain, general health, vitality, social functioning, emotional, and mental health) from the patient's perspective. All scores were transformed onto a scale from 0 to 100 with higher scores indicating better functioning. The MC-QoL is a disease-specific QoL tool developed specifically for use in patients with ISM and cutaneous mastocytosis. The MC-QoL evaluated 27 items organized into four domains: symptoms, emotions, social life/functioning, and skin. The items were evaluated on a five-point scale (0 to 4), with a recall period of 2 weeks. The total and domain raw scores were calculated and transformed to a 0 to 100 scale, with higher scores indicating a worse health-related QoL impairment. The EQ-5D-5L is a standardized instrument for measuring generic health status made up of two components: a health state descriptive system and a Visual Analogue Scale (EQ-VAS). The health state descriptive system was comprised of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patients self-rated each dimension based on a five-point scale (1 to 5), either in terms of capability (from "no problems" to "unable" to "achieve activity") or severity (from "no" to "extremely"). The EQ-VAS measured self-rated overall health on visual scale where endpoints are labelled 'worst health you can imagine' to 'best health you can imagine'.

The following screening procedures were performed and entered into the CRF:

[0055] Reviewed of inclusion and exclusion criteria.

[0056] Obtained demographic data, including sex, age, race, and ethnicity.

[0057] Completed medical history, including a complete medical and surgical history, targeted history of SM, any prior mastocytosis in skin, concomitant medications (including BSC), prior antineoplastic mastocytosis treatments, the duration and response to each treatment and reason for discontinuation, if available, prior malignancies, and concurrent illnesses.

[0058] Completed physical examination, including evaluation of skin, head and neck, lymph nodes, heart, lungs, abdomen (including measurement of liver and spleen size by palpation) musculoskeletal, and neurological systems (including focal neurological history and exam).

[0059] Vital signs taken, including weight, height, temperature, pulse, and systolic/diastolic blood pressure.

[0060] ECOG PS.

[0061] 12-lead ECG.

[0062] Clinical laboratory assessments obtained (hematology, coagulation, serum chemistry, and urinalysis).

[0063] Safety assessments (including CBC with differential, serum chemistry and liver function tests)

[0064] Brain imaging by MRI (preferred) or CT scan.

[0065] Serum pregnancy test (women of childbearing potential only) performed within 20 days before the first dose of study drug.

[0066] Documented all anaphylactic episodes treated with epinephrine from the time of informed consent.

[0067] BM biopsy, aspirate, and PB smear.

[0068] Blood sample for KIT D816V mutation testing.

[0069] Skin biopsies of lesional and non-lesional skin in patients with mastocytosis in skin at screening.

[0070] Standardized skin photography in patients with mastocytosis in skin (optional,).

[0071] DXA scan for the evaluation of bone density (optional).

[0072] Record SAEs from the date of informed consent signature through the safety follow-up assessment.

Results

[0073] A total of 226 patients initiated 25 mg once-daily (QD) avapritinib, includes patients from Part 1 who continued avapritinib 25 mg QD or crossed over from placebo to open-label 25 mg QD avapritinib. This also includes patients from Part 2 who received avapritinib 25 mg QD or who crossed over from placebo to avapritinib 25 mg QD.

[0074] Longer-term data with >2 years of follow-up demonstrated durable improvement in symptoms and QoL (SF-12, MC-QoL, EQ-5D, and PGIS measures, and benefit on the PGIC). No new safety concerns were identified with longer exposure compared to initial findings on PIONEER. For details on the initial findings see: Castells M et al. Presented at AAAAI 2023. Oral #627; Gotlib J et al. NEJM Evidence 2023;2(6):EVIDoa2200339. Treatment-related adverse events were similar to the previous report.

[0075] Dose escalation: At baseline shown in table 8 below, patients who dose escalated to 50 mg QD had higher mast cell burden.

Table 8.

Patient demographic	**Patients who did not dose escalate (n=198)**	**Patients who dose escalated (n=28)**	***P*-value**
Age (years), median (range)	51.0 (18-79)	48.4 (22-72)	0.46
Female, n (%)	144 (73)	22 (79)	0.65
ISM symptom burden			
Baseline TSS score, mean (SD)	47.1 (19.7)	54.7 (16.9)	0.04
Mast cell burden			
Median (range) serum tryptase (central), ng/mL	37.5 (3.6-590.4)	55.3 (13.0-444.0)	0.02
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0-60.0)	10.0 (3.0-50.0)	0.003
Median (range) KIT D816V VAF in PB, %	0.28 (0.00-29.2)	1.14 (0.01-41.29)	0.006

Data cut: November 17, 2023

[0076] Avapritinib at a dose of 50 mg QD has promising early efficacy and safety in a subset of patients with ISM who have high disease burden at baseline. At the time of analysis, 28 patients (12%) who received avapritinib 25 mg in PIONEER parts 1 and 2 (n=226) escalated to 50 mg and the median time on avapritinib at the 50 mg dose level was 4.7 months (range, 0.5-16.7). Safety: the only TRAE (treatment-related adverse event) occurring in >1 patient after initiation of the 50 mg dose was peripheral edema (n=4). Efficacy: 21 out of 21 patients who completed two cycles of avapritinib 50 mg had a state-to-improved TSS (18 with improvement in TSS, 3 with stable TSS) with stable TSS defined as <10% increase in TSS. At the time of analysis, no patients had discontinued after protocol-defined dose escalation.

CLAIMS

1. A method of treating a patient with high risk indolent systemic mastocytosis (ISM) with a KIT D816V inhibitor, comprising:

(a) obtaining a blood sample from the patient;

(b) determining whether the patient with ISM has a D816V mutation in KIT having a variant allele frequency (VAF) ≥6% in peripheral blood; and

(c) administering a therapeutically effective amount of a D816V KIT inhibitor to the patient, if the patient is determined to have a KIT D816V VAF ≥6%.

2. The method of claim 1, wherein the VAF is measured by a method selected from the group consisting of Quantitative real-time PCR (Q-PCR), Digital PCR (d-PCR) including droplet digital PCR (ddPCR), Next generation sequencing (NGS), Duplex Sequencing (Duplex-Seq) NS and Super-RCA.

3. The method of claim 1 or 2, wherein the KIT D816V inhibitor is avapritinib.

4. A method of determining whether a patient has high risk indolent mastocytosis (ISM), comprising:

(a) obtaining a biological sample from the patient;

(b) determining whether the patient has a D816V mutation in KIT having a variant allele frequency (VAF) >6% in peripheral blood;

(c) identifying the patient as having high risk ISM, if the patient has a KIT D816V VAF ≥6%.

5. The method of claim 4, wherein the biological sample is peripheral blood.

6. The method of claim 4 or 5, wherein the VAF is measured by a method selected from the group consisting of Quantitative real-time PCR (Q-PCR), Digital PCR (d-PCR) including droplet digital PCR (ddPCR), Next generation sequencing (NGS), Duplex Sequencing (Duplex-Seq) NS and Super-RCA.

7. The method of any one of claims 4-6, wherein the patient is identified as having high risk ISM and administered a therapeutically effective amount of a KIT D816V inhibitor.

8. The method of any one of claims 4-7, wherein the therapeutically effective amount of the KIT D816V inhibitor is a higher amount.

9. The method of any one of claims 4-8, wherein the higher amount is an amount of the KIT D816V inhibitor that is above the amount administered to treat a patient with ISM that is not high risk ISM.

10. The method of any one of claims 4-9, wherein the KIT D816V inhibitor is avapritinib.

11. The method of claim 10, wherein the amount of avapritinib is 50-100 mg QD.

12. The method of claim 11, wherein the amount of avapritinib is 50 mg QD.

13. The method of claim 12, wherein the amount of avapritinib is 100 mg QD.