Long-term Quality of Life and Safety in Patients With Indolent Systemic Mastocytosis Treated With Avapritinib in the PIONEER study

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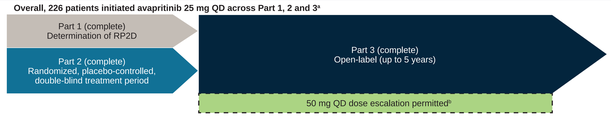
Introduction

- Indolent systemic mastocytosis (ISM) is a chronic clonal mast cell disease primarily driven by the *KIT* D816V mutation in ~95% of cases.[1,2] It is characterized by a broad spectrum of debilitating cutaneous, gastrointestinal, neurological, and musculoskeletal symptoms which can lead to life-threatening anaphylaxis, poor quality-of-life (QoL), and significant morbidity[3–6]
- Historically, the prevalence of systemic mastocytosis (SM) has been estimated at 1 in 10,000 people[7–9] although a recent study suggests that it could affect up to 1 in 5,000 people[10]
- PIONEER (NCT03731260) is a randomized, double-blind, three-part trial examining the efficacy and safety of avapritinib, a potent and selective KIT D816V inhibitor, as a treatment for patients with ISM
- In the placebo-controlled portion of PIONEER, patients treated with avapritinib showed rapid, durable, and clinically meaningful improvements in ISM symptoms and QoL *versus* placebo through 24 weeks of treatment, and avapritinib had a well-tolerated safety profile that was similar to placebo[11,12]
- Based on these outcomes, avapritinib was approved at 25 mg once daily (QD) in adult patients with ISM in the USA and in patients with moderate-to-severe ISM in the EU
- Here we present extended symptom, QoL, and safety findings with avapritinib from PIONEER through median ~3 years of follow-up

Methods

- Patients with moderate-to-severe ISM with symptoms inadequately controlled despite best supportive care (BSC), were enrolled in the randomized, double-blind, placebo-controlled PIONEER study (**Figure 1**)

Figure 1. Study design



[a]n=226, includes patients from Part 1 who continued avapritinib 25 mg QD or crossed over from placebo to avapritinib 25 mg QD. This also includes patients from Part 2 who received avapritinib 25 mg QD or who crossed over from placebo to avapritinib 25 mg. [b]Patients could dose escalate to 50 mg QD in Part 3.
QD, once daily; RP2D, recommended part 2 dose.

- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg QD; the long-term efficacy and safety of avapritinib in this group of patients, as assessed by changes in symptoms and QoL, is presented
  - Symptoms were assessed using the ISM-Symptom Assessment Form (ISM-SAF; ©2018 Blueprint Medicines Corporation), a validated symptom assessment tool specifically developed for evaluation of ISM symptomology based on self-reported severity of 11 ISM symptoms. Scores range from 0–110
  - QoL was assessed using the Mastocytosis Quality-of-Life Questionnaire (MC-QoL), on which scores range from 0–100, where 100 is worst QoL impairment[15,16]
  - Cumulative long-term safety is presented across the entirety of a patient's avapritinib administration on study as of a data cut-off of September 20, 2024
- Per investigator discretion and based on disease burden, dose escalation up to 50 mg QD of avapritinib was permitted in Part 3, safety and efficacy of the 50 mg QD dose were analyzed separately
- A total of 226 patients started avapritinib 25 mg QD as their initial dose in Parts 1, 2, or 3 (termed "the avapritinib population", **Table 1**) with an overall median duration of follow-up (range) of 35.3 (0.7–63.6) months

Table 1. Baseline demographics

Patient demographic	Avapritinib population (n=226)
Age (years), median (range)	49.8 (18–79)
Female, n (%)	166 (73)
Baseline BMI (kg/m²), median (range)	28.1 (17.6–51.4)
ISM symptom burden	
Baseline TSS, mean (SD)	48.1 (19.5)
Mast cell burden	
Median (range) serum tryptase (central), ng/mL	39.2 (3.6–590.4)
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0–60.0)
Median (range) *KIT* D816V VAF in peripheral blood, %	0.39 (undetectable–41.29)

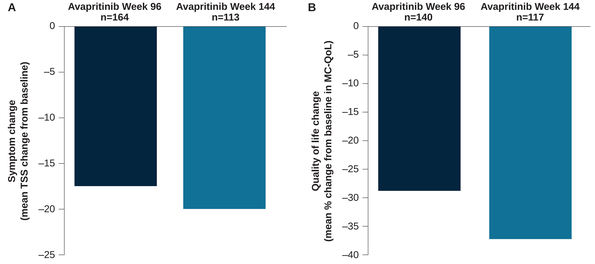
BMI, body mass index; ISM, indolent systemic mastocytosis; SD, standard deviation; TSS, total symptom score; VAF, variant allele frequency.

Results

Efficacy

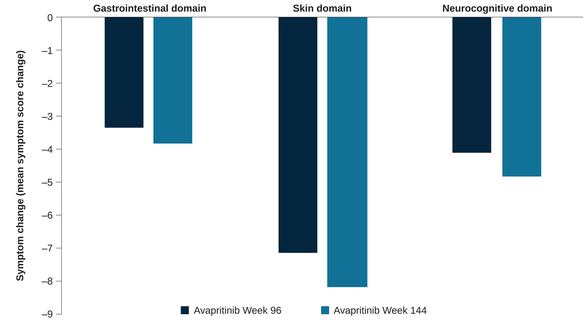
- PIONEER, as the first successful randomized controlled trial of a KIT D816V–targeting agent in ISM, demonstrated that KIT D816V inhibition addresses the breadth of symptoms in patients with ISM[11,12]
- Longer-term efficacy data with median ~3 years of follow-up demonstrate durable improvements in overall symptoms and QoL (per MC-QoL, **Figure 2**)
  - The mean change (standard deviation [SD]) in total symptom score (TSS) from avapritinib first dose was –17.51 (22.25) at Week 96 and –20.07 (20.44) at Week 144
- Continued responses were seen in all symptom domains (**Figure 3**); mean changes (SD) in individual symptoms domains from avapritinib first dose at Weeks 96 and 144 were
  - Gastrointestinal: –3.33 (6.40) and –3.81 (5.77)
  - Skin: –7.11 (8.47) and –8.14 (7.86)
  - Neurocognitive: –4.09 (6.62) and –4.80 (6.42)

Figure 2. Longer-term efficacy for (A) TSS and (B) MC-QoL in the avapritinib patient population at 96 and 144 weeks



MC-QoL, Mastocytosis Quality-of-Life Questionnaire.

Figure 3. Mean change in individual domain symptom scores from baseline in the avapritinib patient population at 96 and 144 weeks



Safety

- The safety profile of avapritinib remained favorable with longer-term median follow-up of three years (**Table 2**)
- No new safety concerns were identified with longer exposure to avapritinib
- Treatment-related adverse events (AEs) were similar to the previous report. Grade ≥3 treatment-related AEs remain limited
- There continues to be a low rate of treatment discontinuation due to treatment-related AEs
- The most frequently reported AE associated with treatment was edema, with the majority of edema events being Grade 1

Table 2. Safety profile of avapritinib

	Avapritinib population (N=226)
Median length of follow-up (range), months	35.3 (0.7–63.6)
Any AEs, n (%)	224 (99)
Any treatment-related AEs, n (%)	168 (74)
Grade ≥3 AEs	103 (46)
Grade ≥3 treatment-related AEs	14 (6)
Serious AEs[a]	45 (20)
Treatment-related serious AEs[b]	3 (1)
Most common TRAEs (≥5% of patients), n (%)	
Peripheral edema	29 (13)
Periorbital edema	22 (10)
Headache	21 (9)
Nausea	18 (8)
Fatigue	16 (7)
Diarrhea	14 (6)
Alopecia	13 (6)
TRAEs leading to discontinuation	7 (3)

[a]One death (Grade 5 serious AE) occurred during the study and was unrelated to treatment; the patient had a medical history of anaphylaxis and atrial fibrillation, and the event was assessed as due to anaphylaxis in the context of atrial fibrillation. [b]Serious TRAEs included peripheral edema (1), gastric hemorrhage (1), and transient loss of vision (1). None of these events led to discontinuation.
AEs, adverse events; TRAEs, treatment-related adverse events.

Patients receiving 50 mg QD avapritinib

- Fifty-seven patients (25%) who received avapritinib 25 mg QD in PIONEER have escalated to 50 mg QD in Part 3
- Patients who dose escalated had a higher mast cell burden at the beginning of avapritinib treatment compared with patients who did not escalate (**Table 3**)

Table 3. Baseline demographics of patients by dose escalation status

Patient demographic	Patients who did not dose escalate (n=169)	Patients who dose escalated (n=57)
Age (years), median (range)	51 (18–77)	50 (22–79)
Female, n (%)	121 (72)	45 (79)
ISM symptom burden		
Baseline TSS score, mean (SD)	46.2 (19.2)	53.6 (19.5)
Mast cell burden		
Median (range) serum tryptase (central), ng/mL	37.6 (3.6–284.0)	45.7 (10.5–590.4)
Median (range) bone marrow biopsy mast cells (central), %	7.0 (1.0–50.0)	10.0 (2.0–60.0)
Median (range) *KIT* D816V VAF in peripheral blood, %	0.24 (undetected–29.18)	0.77 (undetected–41.29)

Data represent baseline values at initiation of avapritinib 25 mg QD.

- 41 out of 44 patients who completed 8 weeks of avapritinib 50 mg QD had a stable-to-improved TSS (34 with improvement in TSS, 7 with stable TSS; whereby stable is defined as 0–10% increase in TSS)
- 30 out of 34 patients who completed 8 weeks of avapritinib 50 mg QD had stable-to-improved MC-QoL (23 with improvement in MC-QoL, 7 with stable MC-QoL; whereby stable is defined as 0–10% increase in MC-QoL)

Table 4. Safety profile of avapritinib in patients after initiation of 50 mg QD[a]

	50 mg dose escalation (n=57)
Median time on avapritinib 50 mg QD (range), months	10.6 (0.3–26.8)
Any AEs, n (%)	34 (60)
Any treatment-related AEs, n (%)	14 (25)
Grade ≥3 AEs	8 (14)
Grade ≥3 treatment-related AEs	0
Serious AEs	5 (9)
Treatment-related serious AEs	0

[a]Includes only new or worsening AEs after initiation of 50 mg QD avapritinib.

- The only treatment-related AE occurring in >1 patient after initiation of the 50 mg QD dose was peripheral edema (n=4)
- No patients discontinued treatment due to AEs after receiving 50 mg QD

Conclusions

- Patients with ISM can suffer from a wide range of debilitating symptoms often not adequately controlled by best supportive care medications
- PIONEER is the first randomized, double-blind, placebo-controlled trial of a highly selective KIT D816V–targeting agent in patients with ISM and led to FDA and EMA approval of avapritinib for the treatment of this disease
- Avapritinib robustly reduces disease-related symptoms across all measured symptom domains and achieves durable improvements in QoL after a median of ~3 years of follow-up
- Avapritinib was generally well-tolerated at doses of 25 mg QD and 50 mg QD, with no new safety concerns identified at either dose
- Avapritinib is an effective and well-tolerated therapeutic option with a favorable long-term benefit-risk ratio across the spectrum of disease seen in patients with ISM

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Conflicts of interest/ disclosures

Dr Castells has served as a consultant for Blueprint Medicines Corporation and is a PI on several clinical trials for Blueprint Medicines Corporation. She has received author fees from UpToDate and the Editorial Board for Annals of Allergy, Asthma & Immunology.

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