Favorable Benefit-Risk Profile of Avapritinib in Indolent Systemic Mastocytosis Is Maintained After 3 Years of Therapy: Longer-Term Analysis of the PIONEER Study

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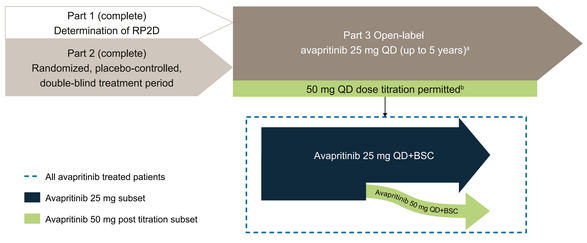
Introduction

- 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]
- The prevalence of systemic mastocytosis (SM) has been estimated at up to 1 in 5000 people[7–10]
- Most patients with ISM rely on symptom-driven best supportive care (BSC) medications which do not treat the underlying driver of ISM
- PIONEER (NCT03731260) is a randomized, double blind, three-part trial examining the efficacy and safety of avapritinib, an oral, 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[11–13]
- 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[14,15]
- Here we present extended findings with avapritinib from PIONEER through median ~3 years of follow-up

Methods

- Patients with moderate-to-severe ISM symptoms who completed the randomized dose-finding (Part 1), or randomized, double-blind, placebo-controlled (Part 2) portions of PIONEER rolled over to the open-label, long-term extension (Part 3) with up to 5-year follow up (**Figure 1**)
- Across all parts of the study, 226 patients initiated avapritinib therapy at 25 mg once daily (QD) + best supportive care (BSC); 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[a]), a validated symptom assessment tool specifically developed for evaluation of ISM symptomology based on self-reported severity of 11 ISM symptoms. Total Symptom Scores (TSS) range from 0–110[16]
  - 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,[17,18] the 12-item Short Form Survey (SF-12), with scores ranging from 0 to 100 (where higher scores indicate fewer limitations on daily life),[19] and the Patient Global Impression of Severity (PGI-S), which scores symptom severity from 0 to 4[20]
  - Long term efficacy and cumulative long-term safety from the initiation of avapritinib at 25 mg QD are presented with a data cut off of September 20, 2024
- Per investigator discretion and based on disease burden, dose titration up to 50 mg QD of avapritinib was permitted in Part 3, safety and efficacy of the 50 mg QD dose were analyzed separately
- Three analyses were conducted
  1. Outcomes from all patients who initiated or rolled over to avapritinib 25 mg QD (**all avapritinib treated patients**)
  2. Outcomes for the same population as (1), but excluding outcomes post-dose titration in the subset of patients that dose titrated to avapritinib 50 mg QD (**avapritinib 25 mg subset**)
  3. Outcomes in the subset of patients who dose titrated to 50 mg QD, using the time of titration as baseline (**avapritinib 50 mg post titration subset**)

Figure 1: Study design and population analysis



[a]n=226, includes patients from Part 1 and Part 2 who started and continued avapritinib 25 mg QD or crossed over from placebo to avapritinib 25 mg QD. [b]Patients could dose titrate to 50 mg QD in Part 3.
BSC, best supportive care; QD, once daily; RP2D, recommended Part 2 dose.

Results

Patient Demographics

- A total of 226 patients started avapritinib 25 mg QD treatment in Parts 1, 2, or 3 (**Table 1**), with an overall median (range) duration of follow-up of 35.3 (0.7–63.6) months, approximately 3 years

Table 1: Baseline demographics

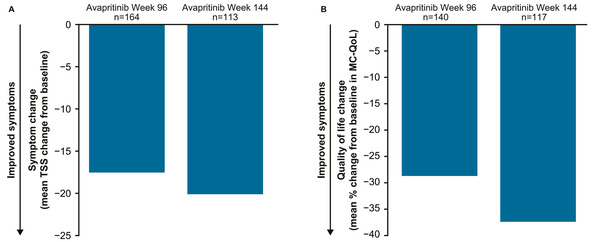
Patient demographic	Avapritinib 25 mg QD (n=226)
Age (years), median (range)	49.8 (18–79)
Female, n (%)	166 (73)
Baseline BMI (kg/m^2), median (range)	28.1 (17.6–51.4)
ISM symptom burden	
Baseline TSS, mean (SD)	48.1 (19.5)
Mast cell burden	
Median (range) serum tryptase (central), ng/mL	39.2 (3.6–590.4)
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.

Efficacy

- PIONEER, the first successful randomized controlled trial of a KIT D816V–targeting agent in ISM, demonstrated that selective KIT D816V inhibition with avapritinib addresses the breadth of symptoms in patients with ISM[8,9]
- Longer-term efficacy data with median ~3 years of follow-up demonstrate durable improvements in overall symptoms and QoL (per MC-QoL)
  - The mean change (standard deviation [SD]) in TSS was −17.51 (22.25) at Week 96 and −20.07 (20.44) at Week 144 in all avapritinib treated patients (**Figure 2**)
  - The mean change (SD) in TSS was −17.89 (21.89) at Week 96 and −21.87 (19.68) at Week 144 in the avapritinib 25 mg QD subset (**Figure 3**)
- Mean percentage change from baseline (SD) in SF-12 data demonstrate sustained responses at Week 96 and 144 in all avapritinib treated patients
  - Physical component: 21.54 (36.04) and 20.84 (32.60)
  - Mental component: 10.63 (31.90) and 12.70 (27.65)
- The proportion of patients with ≥1 improvement in PGI-S was 60% at Week 96 and 64% at Week 144 in all avapritinib treated patients

Figure 2. Longer-term efficacy for (A) TSS and (B) MC-QoL in all avapritinib treated patients at 96 and 144 weeks



Safety

- The safety profile of avapritinib remained favorable with longer-term median follow-up of three years (**Table 2**)
- The most frequently reported adverse event (AE) related to treatment was edema, with the majority of edema events being Grade 1
- Grade ≥3 treatment-related adverse events (TRAEs) in Part 3 remained low and consistent with the randomized portion of the study
- Treatment discontinuations due to TRAEs remained limited occurring in seven patients (3%) over a median of 3 years of treatment

Figure 3. Longer-term efficacy for (A) TSS and (B) MC-QoL in the avapritinib 25 mg QD subset at 96 and 144 weeks

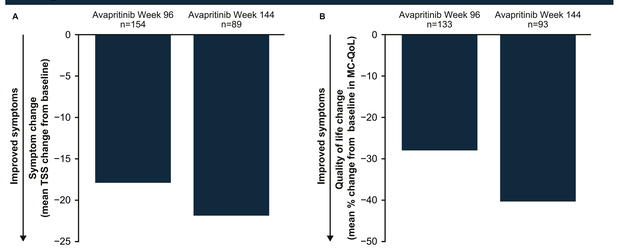


Table 2. Safety profile of avapritinib

	Part 2[a]		Parts 1, 2, 3 combined
	Avapritinib 25 mg QD + BSC (n=141)	Placebo + BSC (n=71)	All patients who initiated avapritinib 25 mg QD + BSC (N=226)[b]
Median length of follow-up (months)[c]	5.6	5.6	35.3
Any AEs, n (%)	128 (91)	66 (93)	224 (99)
Any TRAEs, n (%)	77 (55)	32 (45)	168 (74)
Grade ≥3 AEs	30 (21)	15 (21)	103 (46)
Grade ≥3 TRAEs	3 (2)	2 (3)	14 (6)
Serious AEs	7 (5)	8 (11)	45 (20)[d]
Serious TRAEs	0 (0)	0 (0)	3 (1)[e]
TRAEs leading to discontinuation	2 (1)	1 (1)	7 (3)
Most common TRAEs (≥5% of patients), n (%)			
Peripheral edema	9 (6)	1 (1)	29 (13)
Periorbital edema	9 (6)	2 (3)	22 (10)
Headache	11 (8)	7 (10)	21 (9)
Nausea	9 (6)	6 (8)	18 (8)
Fatigue	6 (4)	2 (3)	16 (7)
Diarrhea	4 (3)	2 (3)	14 (6)
Alopecia	5 (4)	3 (4)	13 (6)
Dizziness	4 (3)	5 (7)	11 (5)

[a]Data cut: June 23, 2022. [b]Data cut: September 20, 2024. [c]Reflects median length of follow up during the indicated study period; 89% of patients receiving avapritinib and 88% of patients receiving placebo in Part 2 rolled over to Part 3. [d]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. [e]Serious TRAEs included transient loss of vision (1), gastric hemorrhage (1), and peripheral edema (1). None of these events led to discontinuation.
AEs, adverse events; BSC, best supportive care; TRAEs, treatment-related adverse events.

Avapritinib 50 mg post titration subset

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

Table 3: Baseline demographics of patients by dose titration status

Patient demographic	Patients who did not dose titrate (n=169)	Patients who dose titrated (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.

Table 4. Safety profile of patients receiving 50 mg QD avapritinib

	50 mg dose titration (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

Data refers to AEs starting or worsening after titration to 50 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; where 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; where stable is defined as 0–10% increase in MC-QoL)
- The only TRAE occurring in >1 patient after initiation of the 50 mg dose was peripheral edema (n=4)
- No patients discontinued treatment due to TRAEs after receiving 50 mg QD

Conclusions

- Patients with ISM can suffer from a wide range of debilitating symptoms often not adequately controlled by BSC 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 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 therapeutic option for patients with ISM with a favorable long-term benefit-risk profile across the spectrum of disease

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Conflicts of interest/ disclosures

Dr Elberink has been involved in an advisory board for Blueprint Medicines Corporation (including the PIONEER study) and has received an Institutional Grant for an IIT of midostaurin from Novartis.

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