# Avapritinib and Bone Health in Indolent Systemic Mastocytosis: Learnings From the PIONEER Trial

Poster Number 527


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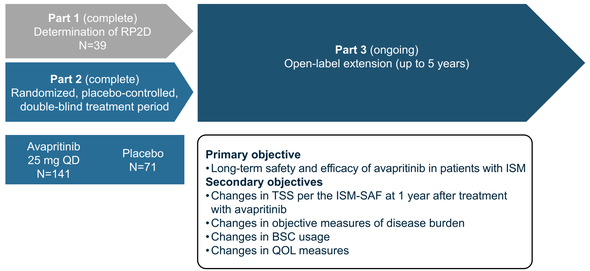
## Introduction

- Indolent systemic mastocytosis (ISM) is a clonal mast cell disease with manifestations driven by the *KIT* D816V mutation in ~95% of patients[1–3]
- Historically, presence of systemic mastocytosis (SM) has been estimated at 1 in 10,000 people[2,4,5] although a recent study suggests that it could affect up to 1 in 5,000 people[6]
- Patients with ISM may experience life-long debilitating symptoms, including life-threatening anaphylaxis and poor quality of life (QOL) with significant morbidity[7–11]
- Musculoskeletal complications, including osteoporosis (~25% of patients), osteopenia (~30% of patients), and fragility fractures (~30% lifetime risk), are also common in these patients[12–14]
  - Serum levels of modulatory bone cytokines have been reported to be significantly increased in ISM associated with osteopenia or osteoporosis[15]
- Avapritinib is a potent, oral inhibitor that selectively targets KIT D816V[16]
- In the PIONEER trial (NCT03731260), avapritinib plus symptom-directed best supportive care (BSC) improved patient symptoms and QOL in patients with moderate to severe ISM[14]
- Avapritinib is approved in the US and Europe for adult patients with ISM based on the outcomes of the PIONEER trial[17,18]
- We examined bone health and changes while on avapritinib at a single site participating in the PIONEER trial

## Methods

- PIONEER is a global, randomized, double-blind, placebo-controlled trial evaluating safety, efficacy, and QOL in adult patients with ISM receiving avapritinib + BSC (avapritinib arm) compared with patients receiving placebo + BSC (placebo arm)
- Adult patients with centrally confirmed ISM with uncontrolled moderate to severe symptoms (total symptom score of ≥28 at screening), despite treatment with ≥2 BSC, were eligible for enrollment
- Upon completion of Part 1 (the dose-finding portion) or Part 2 (the randomized, placebo-controlled, double-blind portion) of the PIONEER study, patients were eligible to receive open-label avapritinib for up to 5 years (Part 3, ongoing; **Figure 1**)
- Physician-reported history of osteoporosis, osteopenia, and medication use was collected at enrollment
- Dual-energy X-ray absorptiometry (DXA) was optional per the study protocol and was performed at the investigator's discretion in a subset of study participants
- Bone mineral density (BMD) data were collected by retrospective review of primary DXA scan reports for all avapritinib-treated trial patients at a single site where DXA scans were consistently performed over time on the same machine (Hologic Horizon)
- DXA scan results at the single site are reported for all patients who had scans done at screening, after 6 months, and after 2 years of avapritinib therapy

### Figure 1: PIONEER study design




BSC, best supportive care; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; QD, once daily; QOL, quality of life; RP2D, recommended Part 2 dose; TSS, total symptom score.

## Results

### Overall study population

- Of 251 patients enrolled across all study sites, 48 (19%) had a medical history of osteopenia and 56 (22%) had a medical history of osteoporosis (**Table 1**)
- Among enrolled patients, concomitant medications included calcium (23%), vitamin D (36%), bisphosphonates (9%), and denosumab (4%)

### Table 1. Baseline demographics and disease characteristics: PIONEER

| | All patients (N=251) | Normal bone mineral density (n=147) | Osteopenia (n=48) | Osteoporosis (n=56) |
|---|---|---|---|---|
| **Age, median years (range)** | 51 (18–79) | 49 (18–76) | 54 (32–77) | 53 (21–79) |
| **Female, n (%)** | 184 (73) | 100 (68) | 36 (75) | 48 (86) |
| **Concomitant medications for bone health, n (%)** | | | | |
| Calcium | 58 (23) | 18 (12) | 18 (38) | 22 (39) |
| Vitamin D | 90 (36) | 34 (23) | 24 (50) | 32 (57) |
| Bisphosphonates | 23 (9) | 1 (<1) | 5 (10) | 17 (30) |
| Denosumab | 9 (4) | 0 | 3 (6) | 6 (11) |
| **Medical history of bone fracture, n (%)** | 29 (12) | 9 (6) | 4 (8) | 16 (29) |
| **BMI, median kg/m² (range)** | 28.3 (17.6–50.1) | 28.6 (17.6–50.1) | 27.7 (21.1–41.2) | 27.2 (18.1–41.5) |
| **T-score, median (range) [n]** | | | | |
| Lumbar spine | –0.90 (–3.60 to 2.80) [147] | –0.50 (–3.20 to 2.50) [83] | –1.35 (–3.10 to 1.70) [34] | –1.65 (–3.60 to 2.80) [30] |
| Femoral neck | –0.97 (–3.30 to 6.10) [110] | –0.40 (–2.40 to 2.50) [59] | –1.30 (–2.60 to –0.20) [25] | –1.75 (–3.30 to 6.10) [26] |
| **T-score, mean (SD) [n]** | | | | |
| Lumbar spine | –0.79 (1.40) [147] | –0.39 (1.23) [83] | –1.03 (1.24) [34] | –1.61 (1.59) [30] |
| Femoral neck | –0.75 (1.26) [110] | –0.35 (1.03) [59] | –1.22 (0.56) [25] | –1.21 (1.83) [26] |

BMI, body mass index; SD, standard deviation.

### Single site analysis

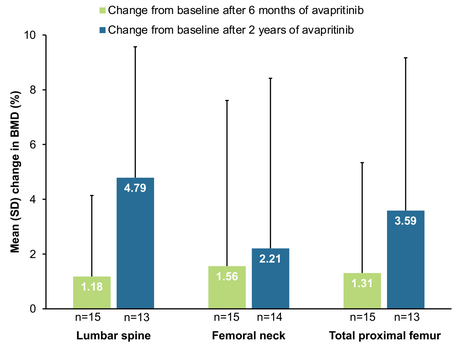
- In 15 patients at a single site with primary DXA results available, 6 (40%) had a baseline T-score between –2.5 and –1 (osteopenia) and 3 (20%) had a T-score of ≤ –2.5 (osteoporosis) (**Table 2**)
- In this cohort, concomitant medications included calcium (40%), vitamin D (67%), and denosumab (13%)
  - No patients in this group received concomitant bisphosphonates
- Mean (SD) BMD increases of 4.79% (4.78), 2.21% (6.21), and 3.59% (5.58) were observed in lumbar spine, femoral neck, and total proximal femur, respectively, after 2 years of avapritinib treatment (**Figure 2**)
- The magnitude of BMD improvement seen in this case series of patients treated with avapritinib is on par with the magnitude of BMD change known to reduce fracture risk in patients with primary osteoporosis[19]
- Changes in BMD in the lumbar spine were particularly notable, because this is the most common site for fracture in patients with ISM[13]

### Table 2. Baseline demographics and disease characteristics: single site

| | Patients with DXA scans available (N=15) |
|---|---|
| **Age, median years (range)** | 52 (33–66) |
| **Female, n (%)** | 12 (80) |
| **Bone health, n (%)** | |
| Normal bone density | 6 (40) |
| Osteopenia | 6 (40) |
| Osteoporosis | 3 (20) |
| **Concomitant medications for bone health, n (%)** | |
| Calcium | 6 (40) |
| Vitamin D | 10 (67) |
| Bisphosphonates | 0 |
| Denosumab | 2 (13) |
| **Medical history of bone fracture, n (%)** | 1 (7) |
| **BMI, median kg/m² (range)** | 27.8 (19.4–33.7) |
| **T-score, median (range) [n]** | |
| Lumbar spine | –0.55 (–2.90 to 0.20) [14] |
| Femoral neck | –1.40 (–2.60 to 0.20) [15] |
| **T-score, mean (SD) [n]** | |
| Lumbar spine | –1.01 (1.05) [14] |
| Femoral neck | –1.11 (0.79) [15] |

BMI, body mass index; SD, standard deviation.

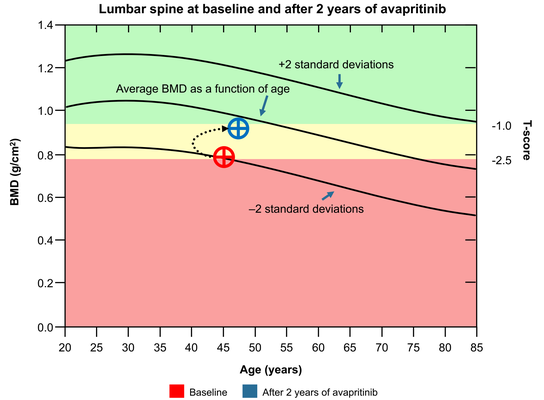
### Figure 2. Aggregated data: lumbar, femoral neck, and total proximal femur T-scores from a single site




### Patient case

- 45-year-old female diagnosed with ISM at the age of 28
- Prior treatments for ISM included interferon alpha and hydroxyurea
- She enrolled in the PIONEER study on July 12, 2021
- She had a medical history of osteopenia and was receiving concomitant medications to support bone health, including calcium/vitamin D since 2019
- The patient experienced increases in lumbar spine, femoral neck, and total hip BMD and T-score as measured by DXA scan after 2 years of avapritinib therapy (**Figure 3**, **Table 3**)

### Figure 3. Change in the patient's lumbar spine BMD and T-score during the PIONEER study




Change in the patient's lumbar spine BMD at baseline and after 2 years of avapritinib. BMD (left y-axis) and T-score (right y-axis) are plotted as a function of patient age. Green-, yellow-, and red-shaded regions represent BMD/T-score values that correspond to healthy bone density (T-score ≥ –1), osteopenia (T-score between –1 and –2.5), and osteoporosis (T-score ≤ –2.5), respectively. Solid black lines indicate the average (± 2 standard deviations) BMD as a function of age. The circled cross indicates the patient's age and BMD.
BMD, bone mineral density.

### Table 3. Change in the patient's lumbar spine, femoral neck, and total hip BMD and T-score during the PIONEER study

| | Time on avapritinib treatment | |
|---|---|---|
| | 6 months | 2 years |
| **Percent change from baseline in BMD** | | |
| Lumbar spine | +2.04 | +16.41 |
| Femoral neck | +7.36 | +8.80 |
| Total hip | +7.13 | +11.58 |
| **Absolute change from baseline in T-score** | | |
| Lumbar spine | +0.2 | +1.2 |
| Femoral neck | +0.5 | +0.5 |
| Total hip | +0.6 | +0.9 |

BMD, bone mineral density.

## Conclusions

- Osteoporosis and osteopenia are prominent features of ISM and were prevalent in the PIONEER population
- In a case series of avapritinib-treated patients followed with serial DXA scans at a single site, retrospectively assessed increases in mean BMD were observed in the lumbar spine (+4.79%), femoral neck (+2.21%), and total proximal femur (+3.59%) after 2 years of treatment
- These hypothesis-generating results examining the impact of avapritinib plus BSC on bone health in ISM provide an impetus for pursuing longitudinal follow-up studies assessing BMD in a larger cohort of patients with ISM
- The ongoing phase 2/3 HARBOR study examining elenestinib for the treatment of ISM will prospectively assess the effects of this selective KIT D816V inhibitor on BMD, a key disease feature, in patients with ISM (see poster #533)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### Disclosures

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