Results from PIONEER: A Randomized, Double-blind, Placebo-controlled, Phase 2 Study of Avapritinib in Patients with Indolent Systemic Mastocytosis (ISM)

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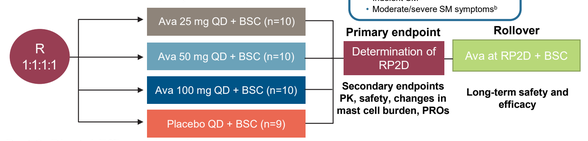
Background and methods

- Systemic mastocytosis (SM) is a rare condition caused by accumulation of clonal mast cells, mainly associated with D816V mutation in the activation loop of KIT[1,2]
- Avapritinib is a selective, potent inhibitor of KIT D816V and has shown objective and symptomatic responses in SM[3–5]
- PIONEER (NCT03731260) is a randomised, double-blind, placebo-controlled phase 2 study of avapritinib vs placebo in patients with indolent SM **(Figure 1)**
  - Efficacy assessed using the Indolent Systemic Mastocytosis-Symptom Assessment Form (ISM-SAF), a patient-reported outcome construct designed with input from disease experts, patients and regulatory authorities to support regulatory approval[6]
  - Symptoms scored from 0 (none) to 10 (worst) and included abdominal pain, diarrhoea, nausea (gastrointestinal group), spots, itching, flushing (skin group), brain fog, headache, dizziness (neurocognitive group), bone pain and fatigue

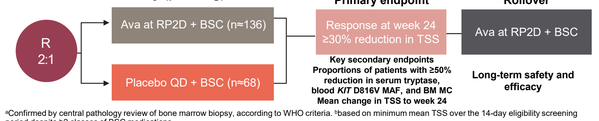
Figure 1: PIONEER study design

Data cut-off date was 27 December 2019

Part 1: Dose escalation (fully enrolled)



Part 2: Pivotal Efficacy (pending)



[a]Confirmed by central pathology review of bone marrow biopsy, according to WHO criteria. [b]based on minimum mean TSS over the 14-day eligibility screening period despite ≥2 classes of BSC medications.
Ava, avapritinib; BM, bone marrow; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MAF, mutation allele fraction; MC, mast cells; PK, pharmacokinetics; PROs, patient reported outcomes; QD, once daily; R, randomise; RP2D, recommended phase 2 dose; TSS, total symptom score.

Results

Patients

- Patient baseline characteristics are shown in **Table 1**
- Overall, 95% (37/39) patients enrolled by data cut-off were continuing on the study
- Two patients discontinued due to patient decision and protocol non-compliance (n=1 each); median (range) time on study was 18 weeks (1–36)

Safety

- No grade 4 or 5 adverse events (AEs) were reported in the study; no grade 3 AEs were reported in the 25 mg cohort (**Table 2**)
- No patients discontinued due to AE or progression to advanced SM
- No neutropenia, anaemia, thrombocytopaenia, or intracranial bleeding
- One grade 3 cognitive disorder in the 100 mg cohort was resolved following dose modification; patient remains on treatment at 25 mg

Table 1: Baseline characteristics

Patient demographics, n (%)		All doses (N=39)
Median age (range), years		51 (21–75)
Female		30 (77)
ECOG PS	0	12 (31)
	1	19 (49)
	2	8 (21)
Mast cell burden, n (%)		
Central diagnosis of indolent SM		39 (100)
Median tryptase, ng/mL (central), range		45, 6–416
Median BM core biopsy MC, % (central) range		10, 1–60
MC aggregates present, %		90

KIT D816V mutation	Local[a]	Central NGS[b]	Central ddPCR[c]
n (%) detected	31 (80)	11 (28)	37 (95)
Median MAF, % (range)	–	11 (1.9–32)	0.36 (0.16–30.22)

SM therapy, n (%)	
Prior cytoreductive therapy	6 (15)
Midostaurin, imatinib, dasatinib, masitinib	5 (13)
Interferon alpha	1 (3)
Baseline supportive care medications, median (range)	4 (2–9)
H1 blockers, n (%)	37 (95)
H2 blockers, n (%)	30 (77)
Leukotriene receptor antagonists, n (%)	23 (59)
Proton pump inhibitors, n (%)	18 (46)
Cromolyn sodium, n (%)	12 (31)
Corticosteroids, n (%)	6 (15)
Omalizumab, n (%)	9 (23)

[a]Local quantitative and qualitative KIT testing of bone marrow and/or blood, various methods and sensitivities. [b]NGS targeted myeloid panel (central) in blood, algorithmic calling sensitivity to 1.9% MAF. [c]Digital droplet PCR in blood (central), sensitivity to 0.02% MAF, detected: positive at screening or C1D1, Median MAF and range at C1D1 in those with any detection.
BM, bone marrow; C1D1, cycle 1 day 1; ECOG PS, Eastern Cooperative Oncology Group performance status; MAF, mutation allele fraction; MC, mast cells; NGS, next generation sequencing; ddPCR, droplet digital polymerase chain reaction; SM, systemic mastocytosis.

Table 2: Tolerability of avapritinib across all doses

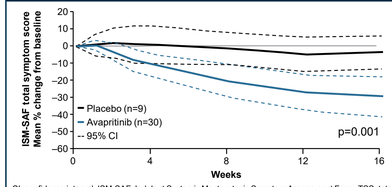
AEs in ≥15% of placebo or combined avapritinib arms (any grade)	Placebo (n=9)		Avapritinib 25 mg (n=10)		Avapritinib 50 mg (n=10)		Avapritinib 100 mg (n=10)	
	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3	Any grade	Grade 3
Patients with ≥1 AE, %	89	22	100	0	80	20	90	40
Nausea	22	0	10	0	60	10	40	0
Dizziness	22	0	30	0	30	0	40	0
Headache	11	0	30	0	30	10	30	10
Diarrhoea	11	0	0	0	40	10	30	10
Fatigue	11	0	40	0	10	0	10	0
Face oedema	0	0	10	0	0	0	40	0
Peripheral oedema	0	0	10	0	20	0	20	0
Periorbital oedema	0	0	0	0	20	0	30	0
Bone Pain	22	0	0	0	0	0	0	0
Arthralgia	22	0	0	0	0	0	0	0

AE, adverse event.

Efficacy

- Avapritinib significantly improves individual symptoms vs placebo (**Figure 2**)
- **Avapritinib 25 mg once daily (QD) dose was selected as the recommended phase 2 dose**
- Avapritinib 25 mg QD achieved similar reduction to 100 mg QD (**Figure 3**) and improved most bothersome symptom groups by week 16 (**Figure 4**)
- Avapritinib 25 mg QD improved individual symptoms vs placebo (**Figure 5**)
- Avapritinib 25 mg QD improved quality of life vs placebo per Mastocytosis Quality of Life (MC-QoL) (**Figure 6**)
- Objective reductions in mast cell burden observed at 25 mg QD (**Figure 7**)

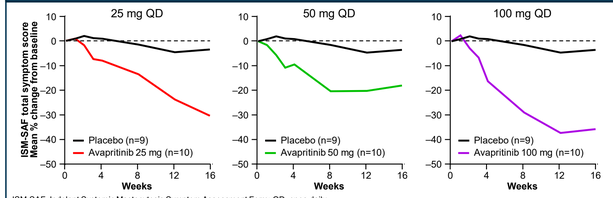
Figure 2: Symptom burden at week 16 (all doses)



- ~30% mean symptom reduction at 16 weeks in avapritinib treated patients measured by ISM-SAF TSS
- ~3% mean symptom reduction in placebo
- Difference is statistically significant (p=0.001) at 16 weeks of therapy

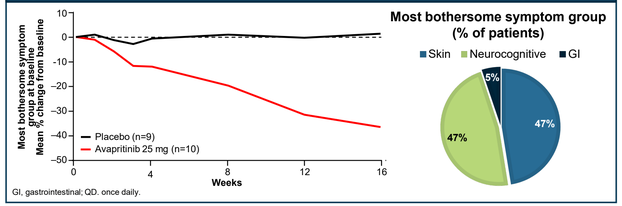
CI, confidence interval; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; TSS, total symptom score.

Figure 3: Symptom burden at week 16 (25 mg, 50 mg, 100 mg QD)



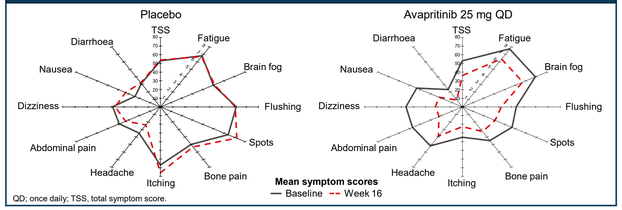
ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; QD, once daily.

Figure 4: Improvements in most bothersome symptoms (25 mg QD)



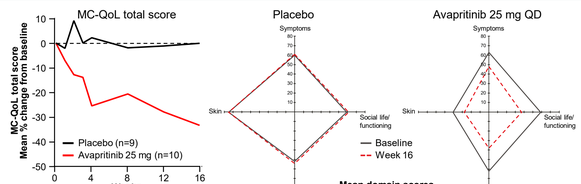
GI, gastrointestinal; QD. once daily.

Figure 5: Symptom reduction by week 16



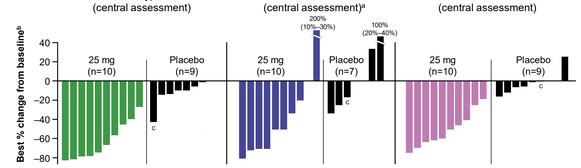
QD; once daily; TSS, total symptom score.

Figure 6: Quality of life improvements by week 16



MC-QoL; Mastocytosis Quality of Life; QD, once daily.

Figure 7: Mast cell burden in 25 mg vs placebo



[a]Bone marrow mast cell assessment in SM may have variability in sampling due to patchy nature of disease. No patient on study has progressed to advanced disease. [b]Serum tryptase assessments at weeks 1, 2, 3, 4 and every 4 weeks thereafter; bone marrow assessment at week 12; mutation burden assessments at weeks 2 and 4 and every 4 weeks thereafter. [c]Patient received high dose IV steroids. IV, intravenous; SM, systemic mastocytosis.

Conclusions

- In this phase 2 study, QD avapritinib treatment resulted in a statistically significant reduction in total symptom score (p=0.001) at 16 weeks of therapy
- Avapritinib has a favorable safety profile in patients with indolent SM
- Avapritinib 25 mg once daily was selected as the recommended phase 2 dose; clinically meaningful improvements at 16 weeks were reported at this dose
  - Reductions in bone marrow MC burden, serum tryptase and blood *KIT* D816V allele fraction
  - Improvements in clinical outcomes and quality of life
- Avapritinib, a selective, potent KIT D816V inhibitor, demonstrates potential as a new treatment for patients with indolent SM

References

1. Valent P *et al. Blood.* 2017;129(11):1420–1427; 2. Pardanani A *et al. Am J Hematol.* 2019;94:363–377; 3. Evans EK *et al. Sci Trans Med.* 2017;9eaao1690; 4. Radia D *et al.* Presented at 24th European Hematology Association Congress, Amsterdam, Netherlands, July 13–16, 2019; 5. Gotlib JR *et al. Blood.* 2018;132(Suppl 1):351; 6. Sheikh A *et al. Value Health.* 2019;22(Suppl 3):S867–S868.

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