Avapritinib Impacts the Plasma Inflammatory Proteome in Patients With Indolent Systemic Mastocytosis (ISM)

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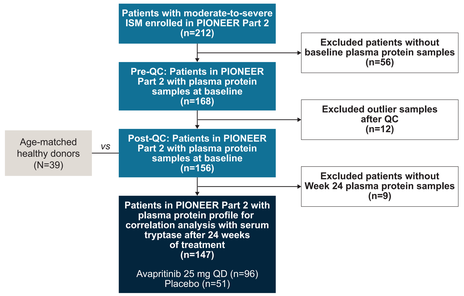
Introduction

- The prevalence of systemic mastocytosis (SM) has been estimated at up to 1 in 5,000 people[1]
- Indolent systemic mastocytosis (ISM), the most common subtype of SM, is a clonal mast cell (MC) disease driven by the *KIT* D816V mutation in ~95% of patients[2–5]
- Patients with ISM often experience life-long debilitating symptoms across multiple organ systems[6–10]
  - These symptoms are likely due to a combination of direct MC organ infiltration, MC activation and mediator release, and inflammatory immune system alterations promoted by aberrant MCs[10]
- Avapritinib is a potent, oral inhibitor that selectively targets the KIT D816V mutation,[11] with approximately 30-fold selectivity for the mutant KIT protein over the wild-type KIT protein[12]
- In the PIONEER trial (NCT03731260) studying patients with moderate-to-severe ISM, avapritinib significantly reduced symptom burden and biomarkers of MC burden, compared with placebo[13]
  - Avapritinib has been approved in the USA and Europe for adult patients with ISM based on these findings[14,15]
- The clonal expansion and activation of MCs with consequent release of mediators results in inflammatory changes which impact tissues and cells to an extent that has not been explored
- To further explore this, we leveraged the large and well-characterized population of patients enrolled in PIONEER to conduct high-throughput profiling of the inflammatory plasma proteome

Methods

- The Olink® Explore 384 Inflammation panel (Uppsala, Sweden) measured 363 well-established plasma proteins in plasma samples from patients in PIONEER and healthy donors (**Figure 1**)
- Plasma samples from age-matched healthy donors (n=39) were assessed as controls and compared with baseline plasma protein samples from patients in PIONEER (N=156)
- Plasma protein measurements below the lower limit of quantification (LLOQ) were imputed as LLOQ values in the analysis
- For baseline plasma protein comparison between healthy donors and patients with ISM, a t-test was performed for each protein and the resulting P-values were adjusted for multiple comparisons using the Benjamini-Hochberg method, false discovery rate (FDR)
  - An FDR of <0.05 was considered significant

Figure 1. Study design



ISM, indolent systemic mastocytosis; QC, quality control; QD, once daily.

- For change from baseline to Week 24 after treatment, a paired t-test was performed for each protein
  - The raw P-values were adjusted for multiple comparisons using the same method above

Results

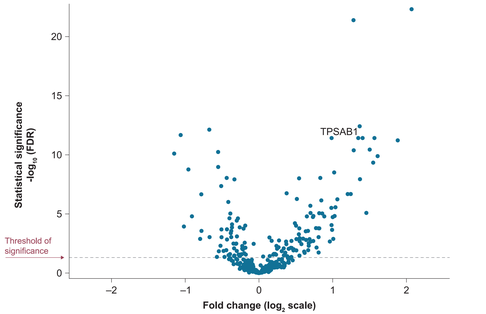
- Baseline demographics are presented in **Table 1**

Table 1. Baseline demographics and disease characteristics

	PIONEER patients who received either avapritinib 25 mg QD or placebo and had suitable samples for plasma protein analysis (n=156)
Age (years), median (range)	52 (22–79)
Female, n (%)	119 (76)
ISM symptom burden	
Baseline ISM-SAF TSS, mean (SD)	51.7 (19.9)
MC burden	
Median (range) baseline serum tryptase, ng/mL	44.3 (3.6–501.6)
Median (range) baseline BM MCs, %	7.0 (1.0–70.0)
Median (range) baseline *KIT* D816V VAF in peripheral blood, %	0.42 (undetectable–36.7)

BM, bone marrow; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form (© 2018 Blueprint Medicines Corporation); MC, mast cell; SD, standard deviation; TSS, total symptom score; VAF, variant allele frequency.

Figure 2. Comparison of baseline plasma proteins present in patients with ISM *vs* healthy donors



FDR, false discovery rate.

- At baseline, 156/363 proteins were significantly different in patients with ISM *versus* healthy donors (FDR <0.05) (**Figure 2**)
- After 24 weeks of avapritinib therapy, 76/363 proteins differed significantly from baseline (FDR <0.05) (**Figure 3**)

Figure 3. Plasma protein changes in patients in PIONEER treated with 24 weeks of avapritinib

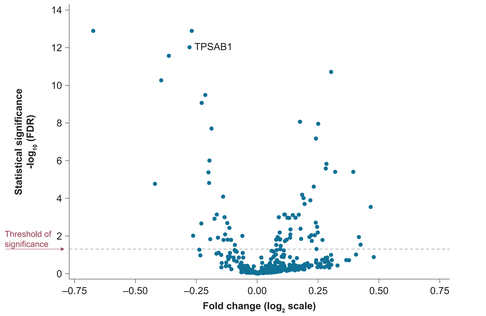
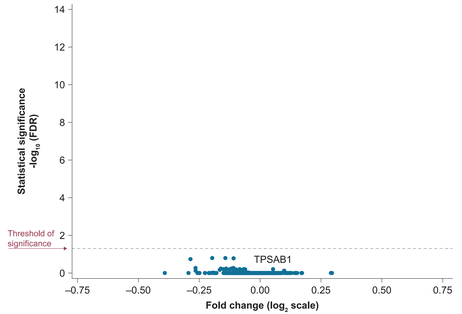
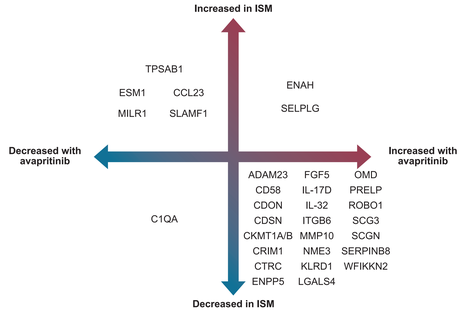


Figure 4. Plasma protein changes in patients in PIONEER receiving 24 weeks of placebo



- No proteins showed significant changes in placebo-treated patients (**Figure 4**)
- Out of the 156 proteins identified as ISM-specific, six significantly decreased with avapritinib therapy and 25 significantly increased (**Figure 5**)

Figure 5. Overlap between plasma proteins significantly different in patients with ISM *versus* plasma proteins significantly changed by avapritinib treatment for 24 weeks



Results

- Our analysis identified significantly higher levels of tryptase (TPSAB1) in patients with ISM *versus* healthy donors and also identified significant decreases in tryptase in patients receiving avapritinib, validating the ability of this technique to detect clinically meaningful differences in the levels of circulating plasma proteins
- Cytokine analysis identified multiple proteins previously linked to MC biology and SM. For example, CCL23 is produced by MCs and its levels correlate with the severity of disease, with the highest levels seen in patients with advanced SM[16,17]
  - Avapritinib significantly reduced the levels of elevated CCL23 seen in patients with ISM
- Out of the 31 proteins significantly changed by avapritinib, 28 were changed towards normal levels (**Figure 5**)

Conclusions

- Many differences are seen between the plasma proteome of patients with ISM *versus* healthy individuals, highlighting the immune dysregulation in this disease
- This analysis provides insight into the effects of avapritinib treatment on the inflammatory plasma proteome
- We provide evidence that circulating inflammatory proteins could serve as biomarkers of ISM disease burden and also may identify new potential therapeutic targets for its treatment

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Disclosures

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For all author disclosures, please contact medinfo@blueprintmedicines.com.

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