# Favorable Efficacy and Safety Profile of Avapritinib Is Maintained in the Context of Omalizumab Treatment

Poster Number R291


**Cem Akin,[1] Karin Hartmann,[2,3] Sigurd Broesby-Olsen,[4] Tracy I. George,[5] Frank Siebenhaar,[6,7] Benjamin Lampson,[8] Hui-Min Lin,[8] Marcus Maurer[6,7†]**

*[1]University of Michigan, Ann Arbor, MI, USA; [2]Division of Allergy, Department of Dermatology, University Hospital Basel and University of Basel, Basel, Switzerland; [3]Department of Biomedicine, University Hospital Basel and University of Basel, Basel, Switzerland; [4]Odense University Hospital, Odense, Denmark; [5]ARUP Laboratories, Department of Pathology, University of Utah School of Medicine, Salt Lake City, UT, USA; [6]Institute of Allergology, Charité –Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [7]Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology and Allergology, Berlin, Germany; [8]Blueprint Medicines Corporation, Cambridge, MA, USA*

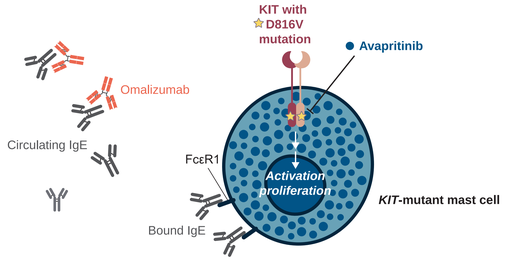
*[†]Deceased.*


## Introduction

- Systemic mastocytosis (SM), including indolent SM (ISM), is a clonal mast cell disease driven by the *KIT* D816V mutation in 95% of cases[1–3]
- ISM is characterized by chronic heterogenous, debilitating symptoms across multiple organ systems that negatively impact quality of life[4–7]
- Avapritinib is a potent, oral, tyrosine kinase inhibitor that selectively targets the KIT D816V mutation[8]
- In PIONEER (NCT03731260), avapritinib significantly improved ISM-Symptom Assessment Form (ISM-SAF®) total symptom scores (TSS) with a well-tolerated safety profile.[8] Based on this study, avapritinib is the first and only approved therapy for adults with ISM in the USA and Europe[9,10]
- Omalizumab, an anti-immunoglobulin E (IgE) antibody, is not approved for use in ISM and does not substantially reduce ISM-related biomarkers, but is still used as symptom-directed best supportive care (BSC) in the real-world clinical setting in some patients with SM[11]
  - Omalizumab was allowed as BSC in PIONEER
  - The interaction of omalizumab with IgE and avapritinib with KIT-mutant mast cells is illustrated in **Figure 1**
- Here, we conducted a retrospective analysis of the baseline disease characteristics and treatment course in the subset of patients who received concomitant omalizumab and avapritinib in PIONEER Part 2



### Figure 1. Interaction of omalizumab with IgE and avapritinib with KIT-mutant mast cells

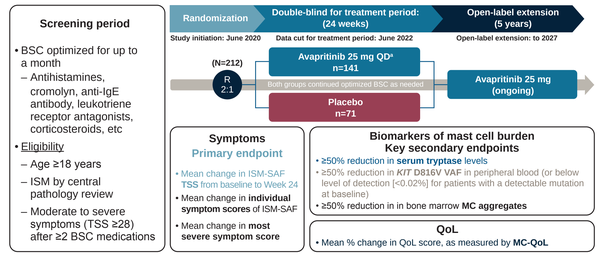



IgE, immunoglobulin E.

## Methods

- PIONEER, a global, randomized, double-blind, placebo-controlled study, evaluated the safety, efficacy, and quality of life (QoL) in adult patients with ISM receiving avapritinib plus BSC, compared with patients receiving placebo plus BSC
- Eligibility criteria included patients with moderate (TSS 28–42) to severe (TSS ≥42) ISM symptoms despite receiving BSC
  - BSC included H1 and H2 antihistamines, leukotriene receptor antagonists, cromolyn sodium, proton pump inhibitors, corticosteroids, and omalizumab
- In Part 2, 212 patients were randomly assigned avapritinib 25 mg orally once daily (QD) plus BSC (avapritinib; n=141) or placebo plus BSC (placebo; n=71) for 24 weeks. After 24 weeks of treatment, patients were eligible to receive open-label avapritinib 25 mg QD for up to 5 years in Part 3 (**Figure 2**)
- Patients' BSC medications were stabilized for up to 4 weeks prior to initiation of avapritinib/placebo, and were required to be stable for at least 14 days without a flare up of symptoms before baseline TSS was calculated
  - Omalizumab was continued on study as BSC, per investigator discretion
- The ISM-SAF is a validated symptom assessment tool specifically developed for evaluation of ISM symptomology[12–14]
  - TSS is based on the severity of 11 ISM symptoms
  - The ISM-SAF was developed over 8 years with input from patients, disease experts, and global regulatory agencies[13]

### Figure 2. PIONEER study design




[a]The recommended dose of avapritinib for Part 2 and Part 3 was identified based on efficacy and safety results from Part 1 that included four blinded, randomized cohorts: 25 mg avapritinib (n=10), 50 mg avapritinib (n=10), 100 mg avapritinib (n=10), and placebo (n=9). BSC, best supportive care; ISM, indolent systemic mastocytosis; ISM-SAF, Indolent Systemic Mastocytosis-Symptom Assessment Form; MC, mast cell; QD, once daily; QoL, quality of life; R, randomized; TSS, total symptom score; VAF, variant allele fraction.

- All patients from Part 2 on avapritinib 25 mg QD and patients from Part 2 on avapritinib 25 mg QD and omalizumab at baseline (and continued on study) were analyzed for change from baseline in ISM-SAF TSS, Mastocytosis Quality of Life Questionnaire (MC-QoL), tryptase levels, and *KIT* D816V variant allele frequency (VAF). Safety was also assessed
- Data from the completed Part 2 PIONEER study (as of June 23, 2022) are presented

## Results

- At baseline, 19 avapritinib-treated patients (13%) were on omalizumab
  - Omalizumab dosing regimens were per investigator discretion and varied widely, with the most common dose being 300 mg subcutaneously (sc) once monthly (QM; n=8) and 300 mg sc every (Q) 2 weeks (Wk) (n=4)
  - Less common omalizumab dosing regimens included 150 mg sc QM (n=1), 150 mg sc Q3Wk (n=1), 450 mg sc Q2Wk (n=1), and 450 mg sc QM (n=1)
  - In 3 patients the omalizumab dose was unknown
- Baseline characteristics and demographics of patients receiving omalizumab were balanced with the overall study population (**Table 1**)

### Table 1. Baseline characteristics

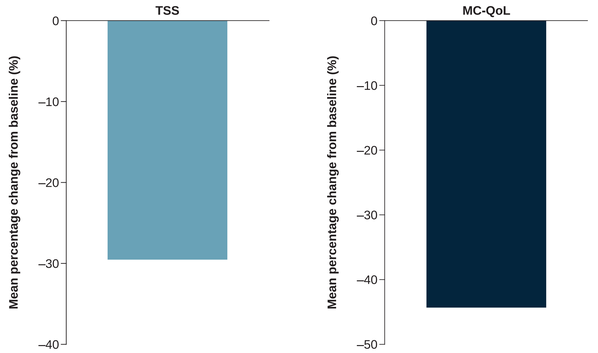
| Patient characteristic | Avapritinib 25 mg QD | |
|---|---|---|
| | Omalizumab at baseline (n=19) | All patients (n=141) |
| Age (years), median (range) | 47 (22–65) | 50 (18–77) |
| Female, n (%) | 13 (68) | 100 (71) |
| **ISM symptom burden** | | |
| TSS, mean (range) | 47.4 (17.6–94.5) | 50.2 (12.1–102.7) |
| **Mast cell burden** | | |
| Median serum tryptase (central), ng/mL (range) | 37.6 (3.6–184.0) | 38.4 (3.6–256.0) |
| Median *KIT* D816V VAF in peripheral blood, % (range)[a] | 0.10 (undetectable–7.25) | 0.39 (undetectable–41.29) |
| *KIT* D816V positivity, n (%) | 14 (74) | 117 (83) |
| Median bone marrow mast cells, % (range) | 5.0 (1.0–30.0) | 7.0 (1.0–50.0) |
| **SM Therapy** | | |
| Prior cytoreductive therapy, n (%)[b] | 6 (32) | 19 (13) |

[a]By digital droplet polymerase chain reaction; limit of detection 0.02%. [b]Cytoreductive therapies included imatinib, masitinib, dasatinib, midostaurin, nilotinib, cladribine, hydroxyurea, interferon alpha, rapamycin, and brentuximab vedotin.
SM, systemic mastocytosis; TKI, tyrosine kinase inhibitor.

## Efficacy evaluation of patients treated with avapritinib and omalizumab

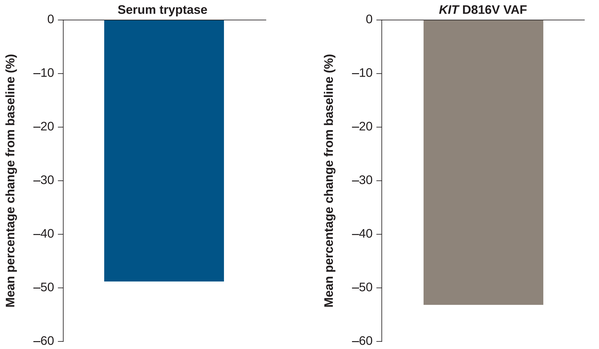
- At Week 24, avapritinib showed improvements in omalizumab-treated patients in mean percentage change from baseline in TSS (–29.3%) and MC-QoL (–44.1%; **Figure 3**)

### Figure 3. Mean percentage change from baseline at Week 24 in TSS and MC-QoL, in patients who received concomitant omalizumab with avapritinib




- ISM disease biomarkers such as serum tryptase levels and *KIT* D816V VAF in omalizumab-treated patients also showed improvements with avapritinib at Week 24, with mean percentage changes from baseline of –48.6% and –52.9%, respectively (**Figure 4**)

### Figure 4. Mean percentage change from baseline in serum tryptase levels and *KIT* D816V VAF at Week 24, in patients who received concomitant omalizumab with avapritinib




## Safety evaluation of avapritinib in patients treated with omalizumab

- Similarly to the overall avapritinib-treated population in Part 2, avapritinib 25 mg QD was well tolerated in patients who received omalizumab at baseline (**Table 2**)

### Table 2. Summary of AEs in Part 2

| | Avapritinib 25 mg QD | | Placebo |
|---|---|---|---|
| | Omalizumab at baseline (n=19) | Overall patients (n=141) | Overall population (n=71) |
| Any AEs, n (%) | 19 (100)[a] | 128 (91)[a] | 66 (93) |
| Grade ≥3 AEs | 5 (26)[a] | 30 (21)[a] | 15 (21) |
| Any grade TRAEs, n (%)[b] | 8 (42) | 77 (55) | 32 (45) |
| Grade ≥3 TRAEs[b] | 1 (5) | 3 (2) | 2 (3) |
| Treatment-related SAEs, n (%)[b] | 0 (0) | 0 (0) | 0 (0) |
| TRAEs leading to discontinuation | 1 (5) | 2 (1) | 1 (1) |

[a]AEs refer to treatment-emergent AEs, defined as any AE that occurred between day 1 of Part 2 through to a day prior to day 1 of Part 3 if the patient crossed over to Part 3; if the patient did not cross over, then through 30 days after the last dose of study drug. [b]Treatment-related AEs/SAEs refer to AEs that were, in the opinion of the treating investigator, related to avapritinib use.
AEs, adverse events; SAEs, serious adverse events; TRAEs, treatment-related adverse event.

- Most adverse events (AEs) were Grade 1 or 2, and there was a low rate of discontinuations
- The only AE deemed as related to avapritinib treatment that occurred in >1 patient after 24 weeks of concomitant omalizumab and avapritinib was periorbital edema (n=2/19)

## Conclusions

- Patients receiving avapritinib with concomitant omalizumab demonstrated improvements in TSS, MC-QoL, *KIT* D816V VAF, and serum tryptase
- Avapritinib was well tolerated in patients receiving avapritinib with concomitant omalizumab, similar to the overall avapritinib-treated patient population in Part 2
- These results demonstrate that avapritinib can provide benefit to patients already receiving omalizumab, highlighting the favorable benefit-risk profile of avapritinib
- Treatment with avapritinib should be considered in patients with ISM, including those who are receiving omalizumab


### References

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