PIONEER: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of Avapritinib in Patients with Indolent or Smoldering Systemic Mastocytosis with Symptoms Inadequately Controlled with Standard Therapy

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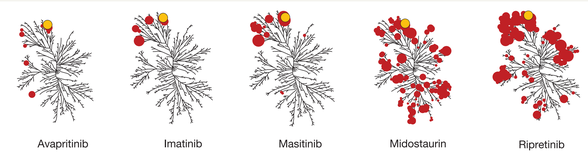
BACKGROUND

- Patients with systemic mastocytosis (SM) can suffer from severe mast cell (MC) mediator symptoms, caused by MC proliferation and hyperactivation due to the *KIT* D816V mutation[1]
- Symptoms may include skin lesions, pruritus, diarrhea, anaphylaxis, brain fog, and bone pain, which can be severely debilitating and have a profoundly negative impact on quality of life
- Polypharmacy with multiple symptomatic treatments (e.g., antihistamines, ketotifen, omalizumab, cromolyn sodium, leukotriene inhibitors, and corticosteroids) are used to control symptoms with varying degrees of efficacy; however, these treatments fail to impact MC burden, and there are no approved disease-modifying therapies
- Patients with indolent (ISM) and smoldering SM (SSM) typically have a single driver gain-of-function *KIT* mutation making them promising candidates for KIT D816V inhibitor therapy
- Avapritinib is an investigational, oral, potent, and highly selective KIT D816V inhibitor[2] **(Figure 1)**

Figure 1. Avapritinib kinome selectivity and potency on KIT D816V[2]

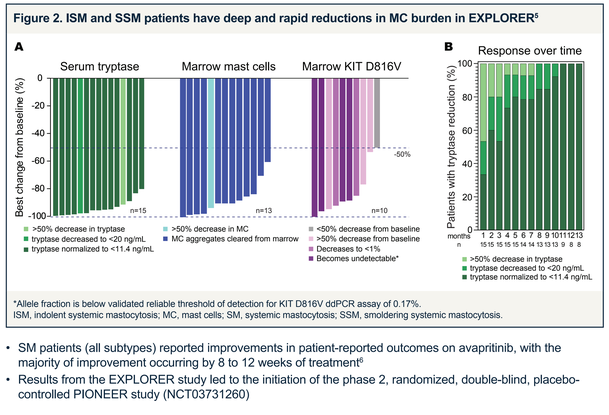


KIT D816V biochemical IC_{50}				
Avapritinib[2]	Imatinib[2]	Masitinib[3]	Midostaurin[2]	Ripretinib[3]
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Biochemical binding by DiscoverRX at 3 µM. Kinome illustrations reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) (www.cellsignal.com). Blueprint Medicines is not responsible for its content.

- In an ongoing, phase 1, open-label, dose-escalation study in SM (EXPLORER; NCT02561988), avapritinib was associated with deep reductions in MC burden, from the first dose escalation cohort of 30 mg daily (QD)[4]
- Patients with ISM and SSM (n=15) had deeper and more rapid responses than those with advanced SM:[5]
  - 87% normalized tryptase, 92% cleared MC aggregates and the *KIT* D816V mutation became undetectable in 40% **(Figure 2A)**
  - Every ISM and SSM patient had >50% serum tryptase reduction by 1 month; every patient at 11+ months of therapy had normal tryptase levels. Tryptase reduction typically preceded improvements in symptom burden **(Figure 2B)**

Figure 2. ISM and SSM patients have deep and rapid reductions in MC burden in EXPLORER[5]



*Allele fraction is below validated reliable threshold of detection for KIT D816V ddPCR assay of 0.17%.
ISM, indolent systemic mastocytosis; MC, mast cells; SM, systemic mastocytosis; SSM, smoldering systemic mastocytosis.

- SM patients (all subtypes) reported improvements in patient-reported outcomes on avapritinib, with the majority of improvement occurring by 8 to 12 weeks of treatment[6]
- Results from the EXPLORER study led to the initiation of the phase 2, randomized, double-blind, placebo-controlled PIONEER study (NCT03731260)

OBJECTIVE

The phase 2 PIONEER study is being conducted to:

- Identify the recommended phase 2 dose (RP2D) in ISM (part 1)
- Investigate efficacy of avapritinib vs placebo in patients with ISM and SSM (part 2)
- Further characterize the safety and efficacy of long-term treatment with avapritinib (part 3; rollover)

METHODS

- PIONEER is a multicenter, randomized, double-blind, placebo-controlled, phase 2 study of patients with ISM or SSM whose symptoms are not adequately controlled by best supportive care (BSC) **(Figure 3)**
- The primary endpoint for part 1 is the determination of the RP2D dose in patients with ISM
- The RP2D will be determined based on change in Total Symptom Score (TSS) from the ISM-Symptom Assessment Form (ISM-SAF) and change in serum tryptase, safety, and pharmacokinetics (PK) at each dose level
- On the ISM-SAF, 11 symptoms (see below) are assessed daily by the patient from 0 (no symptoms) to 10 (worst symptoms) for severity and averaged over 14 days to create the TSS, or the sum of the 11 symptom ratings (range=0–110)
- The primary endpoint for part 2 of the study is the change in ISM-SAF TSS from baseline to week 12
- Patients from both part 1 and part 2 will rollover into receiving open-label avapritinib to study the long-term safety and efficacy of avapritinib (part 3; rollover)

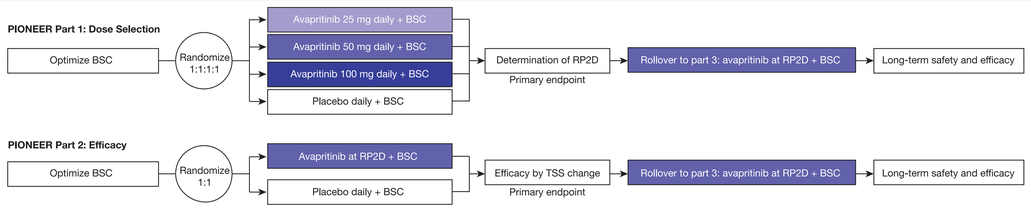
Key Eligibility Criteria

- Age ≥18 years
- Eastern Cooperative Oncology Group performance status 0–2
- ISM or SSM confirmed by central pathology review of bone marrow biopsy, according to World Health Organization criteria
- Moderate-to-severe symptoms based on minimum mean TSS over the 14-day eligibility screening period for assessment of TSS and ≥1 symptom in skin or gastrointestinal domains of the ISM-SAF at baseline
- Failed to achieve symptom control for ≥1 baseline symptom as measured by the ISM-SAF with ≥2 symptomatic therapies administered at optimal doses

	Part 1	Part 2
Goal	Determination of RP2D	Efficacy and Safety
Study Design	**Randomized (10 patients per cohort):** Avapritinib 25 mg daily + BSC Avapritinib 50 mg daily + BSC Avapritinib 100 mg daily + BSC Placebo daily + BSC	**Randomized (36 patients per cohort):** Avapritinib at RP2D + BSC Placebo daily + BSC
Primary Endpoint	RP2D determination	Change in ISM-SAF TSS from baseline to week 12
Secondary Endpoint	Changes in measures of MC burden Changes in measures of skin lesions Quality of life Safety and PK	Changes in measures of MC burden Changes in measures of skin lesions Quality of life Safety and PK
Enrollment	40 patients	72 patients
Duration	12 weeks, then continue until RP2D is determined, then rollover	12 weeks, then rollover
Rollover (Part 3)	All patients receive open-label avapritinib Long-term safety and efficacy	All patients receive open-label avapritinib Long-term safety and efficacy

BSC, best supportive care; GI, gastrointestinal; ISM-SAF, ISM-symptom assessment form; MC, mast cells; PK, pharmacokinetics; RP2D, recommended phase 2 dose; TSS, total symptom score.

Figure 3. PIONEER study schematic



BSC, best supportive care; RP2D, recommended phase 2 dose.

RESULTS

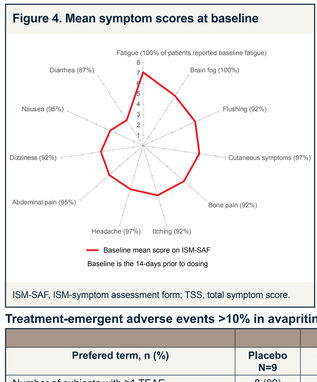
Data cutoff date: November 12, 2019

Baseline demographics, characteristics and disposition

	All doses (N=39)
Patient demographics	
Age (years), mean (SD) Median (range)	49 (13) 51 (21–75)
Sex, n (%), Female Male	30 (77) 9 (23)
ECOG PS, n (%), 0–1 2	31 (79) 8 (21)
Baseline BSC medications recorded, n (%) Median number of medications, n (range) H1 blockers, n (%) H2 blockers, n (%) Leukotriene inhibitors, n (%) Proton pump inhibitors, n (%) Cromolyn sodium, n (%) Corticosteroids, n (%) Omalizumab, n (%) Other supportive care, n(%) Unavailable at time of datacut, n (%)	33 (85) 3 (1–7) 31 (94) 22 (67) 18 (55) 12 (36) 11 (33) 6 (18) 5 (15) 14 (42) 6 (15)
Disease characteristics	
Tryptase, µg/L, Mean (SD) Median (range)	84 (101) 45 (6–416)
Total Symptom Score, 0–110, Mean (SD) Median (range)	53 (19) 52 (19–100)
Bone marrow core biopsy MC, % Mean (SD) Median (range)	16 (15) 10 (1–60)
Bone marrow aspirate MC, % Mean (SD) Median (range)	3 (3) 1 (0–10)
Patient disposition	
Weeks on study, median (range) Still on study, n (%) Discontinued study, n (%) Patient decision, non-compliance	12 (1–30) 37 (95) 2 (5) 1 (1)

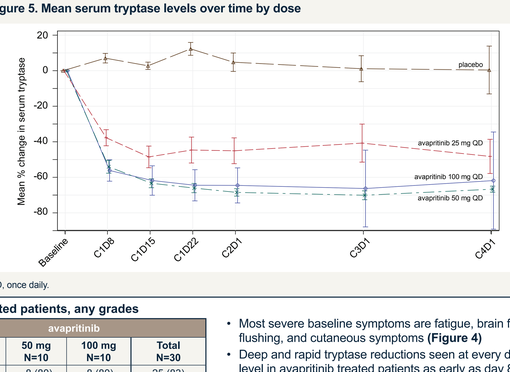
BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MC, mast cell; SD, standard deviation.

Figure 4. Mean symptom scores at baseline



ISM-SAF, ISM-symptom assessment form; TSS, total symptom score.

Figure 5. Mean serum tryptase levels over time by dose



QD, once daily.

Treatment-emergent adverse events >10% in avapritinib-treated patients, any grades

Prefered term, n (%)		avapritinib			
	Placebo N=9	25 mg N=10	50 mg N=10	100 mg N=10	Total N=30
Number of subjects with ≥1 TEAE	8 (89)	9 (90)	8 (80)	8 (80)	25 (83)
Nausea	2 (22)	0	6 (60)	3 (30)	9 (30)
Headache	1 (11)	2 (20)	2* (20)	3* (30)	7** (23)
Dizziness	1 (11)	2 (20)	1 (10)	3 (30)	6 (20)
Diarrhea	1 (11)	0	3 (30)	2* (20)	5* (17)
Fatigue	1 (11)	2 (20)	1* (10)	1 (10)	4* (13)
Face edema	0	1 (10)	0	3 (30)	4 (13)

*Includes 1 ≥grade 3 event. **Includes 2 ≥grade 3 events across all avapritinib doses.
Note: Cognitive disorder occurred in 3 (10%) avapritinib-treated patients. One (3%) was grade 3 and occurred in the 100-mg QD cohort. The event subsequently resolved, and the patient remains on therapy.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

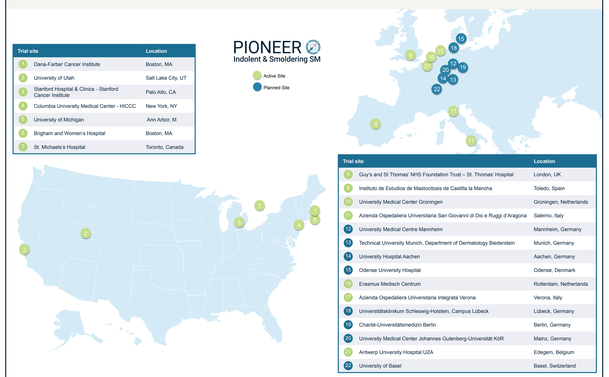
- Most severe baseline symptoms are fatigue, brain fog, flushing, and cutaneous symptoms **(Figure 4)**
- Deep and rapid tryptase reductions seen at every dose level in avapritinib treated patients as early as day 8 **(Figure 5)**
- No intracranial bleeding, thrombocytopenia, or anemia reported in the study
- 3 serious adverse events (SAEs) occurred in 2 (22%) placebo-treated patients: two were mast cell activation flares (reported as diffuse cutaneous mastocytosis and mastocytosis, respectively); the third was a psychogenic seizure
- No SAEs were reported in avapritinib-treated patients
- No patients have discontinued due to an AE

CONCLUSIONS

- At baseline, ISM patients had median of 3 supportive care medications, with the most severe patient reported symptoms being fatigue, brain fog, flushing and cutaneous symptoms
- Patients treated with avapritinib at doses of 25 mg, 50 mg and 100 mg QD showed rapid decreases in serum tryptase, a measure of mast cell burden, by day 8
- Avapritinib was generally well-tolerated in patients with ISM
  - No patient discontinued treatment with avapritinib due to an AE
  - Most common AEs of all grades (avapritinib; placebo) were nausea (30%; 22%), headache (23%, 11%) and dizziness (20%; 11%). No SAEs occurred in avapritinib-treated patients. In placebo-treated patients, 22% had an SAE with mastocytosis flare being predominant
- Additional pending data from part 1 of the PIONEER study, including the change in TSS on the ISM-SAF, will inform selection of the RP2D
- The registration-enabling part 2 of the PIONEER study is anticipated to initiate patient screening in the first half of 2020

More information on our SM trials at www.blueprintclinicaltrials.com/sm/

PIONEER Trial Sites



Trial site	Location
1 Dana-Farber Cancer Institute	Boston, MA
2 University of Utah	Salt Lake City, UT
3 Stanford Hospital & Clinics - Stanford Cancer Institute	Palo Alto, CA
4 Columbia University Medical Center - HICCC	New York, NY
5 University of Michigan	Ann Arbor, M
6 Brigham and Women's Hospital	Boston, MA
7 St. Michaels's Hospital	Toronto, Canada

Trial site	Location
8 Guy's and St Thomas' NHS Foundation Trust – St. Thomas' Hospital	London, UK
9 Instituto de Estudios de Mastocitosis de Castilla la Mancha	Toledo, Spain
10 University Medical Center Groningen	Groningen, Netherlands
11 Azienda Ospedaliera Universitaria San Giovanni di Dio e Ruggi d'Aragona	Salerno, Italy
12 University Medical Centre Mannheim	Mannheim, Germany
13 Technical University Munich, Department of Dermatology Biederstein	Munich, Germany
14 University Hospital Aachen	Aachen, Germany
15 Odense University Hospital	Odense, Denmark
16 Erasmus Medisch Centrum	Rotterdam, Netherlands
17 Azienda Ospedaliera Universitaria Integrata Verona	Verona, Italy
18 Universitätsklinikum Schleswig-Holstein, Campus Lübeck	Lübeck, Germany
19 Charité-Universitätsmedizin Berlin	Berlin, Germany
20 University Medical Center Johannes Gutenberg-Universität KöR	Mainz, Germany
21 Antwerp University Hospital UZA	Edegem, Belgium
22 University of Basel	Basel, Switzerland

As of December 1, 2019. SM, systemic mastocytosis.

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Disclosures

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JG: research funding and honoraria from Blueprint Medicines; has served on advisory committees/ board of directors for Blueprint Medicines
MC: nothing to disclose
MWD: consulting/advisory role for Blueprint Medicines, Pfizer, Ascentage Pharma, TRM, Sangoma, Fusion Pharma, Adelphi, and Sangamo; honoraria from Blueprint Medicines, Pfizer, Takeda, Ascentage Pharma, Humana, Incyte, and Novartis; has served on advisory committees/board of directors for Blueprint Medicines and Takeda
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PvD: employee of Erasmus MC, Rotterdam; speaker's bureau for Novartis
DR: consulting or advisory role for Blueprint Medicines and Novartis; speaker's bureau for Novartis
MT: has served on advisory committees/board of directors for Novartis, Decipherx, and Blueprint Medicines
DJD: honoraria from Amgen, ARIAD, Bristol-Myers Squibb, Incyte, Novartis, Pfizer; research funding from Pfizer
IA-T: nothing to disclose
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KH: nothing to disclose
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