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

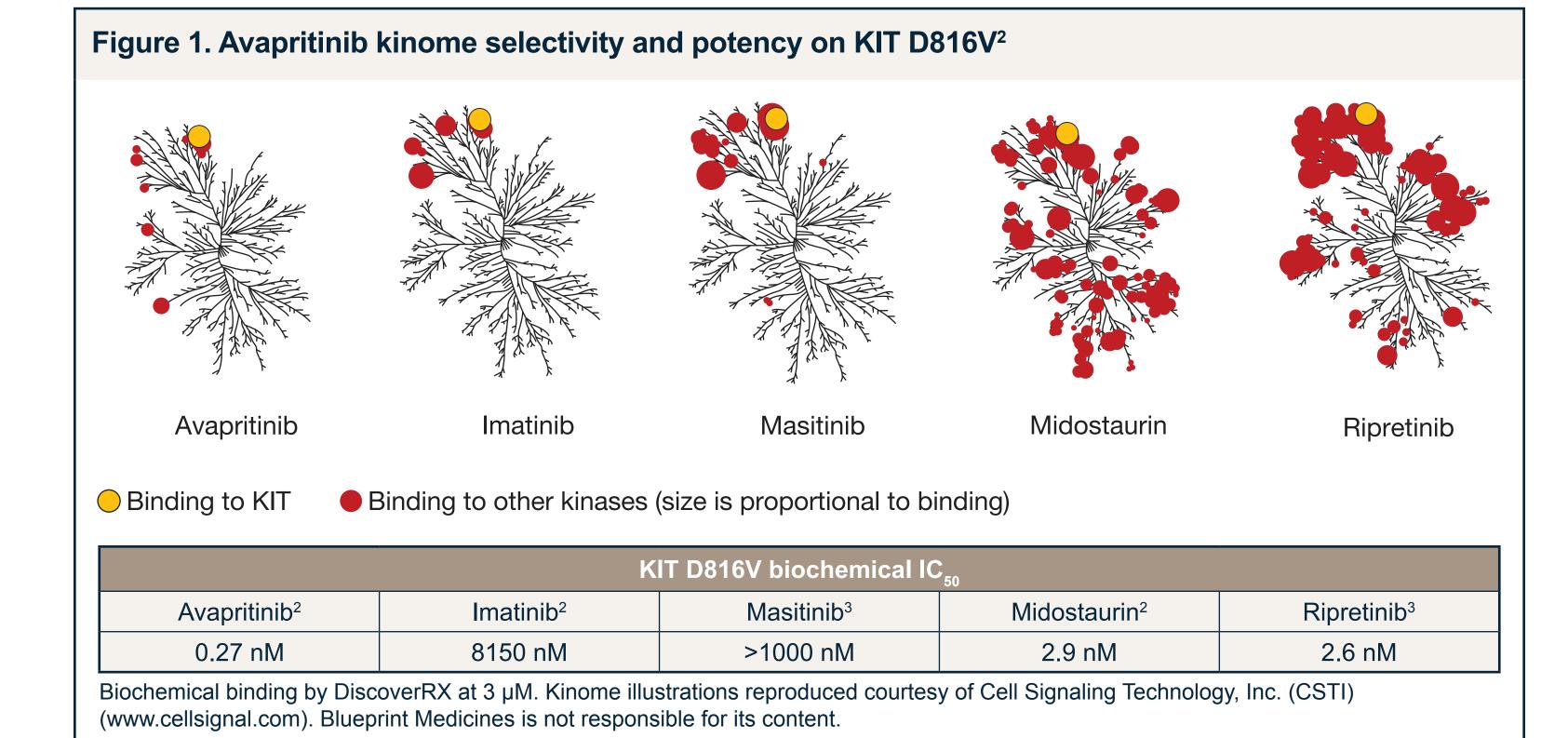
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BACKGROUND

- 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 mutation¹
- 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
- 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 inhibitor² (Figure 1)



- 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 EXPLORER⁵ Response over time Marrow KIT D816\ <50% decrease from baselin</p> 15 15 15 15 15 14 14 13 13 13 9 8 8 ■ tryptase normalized to <11.4 ng/mL</p> ■ Decreases to <1% Becomes undetectable ■ >50% decrease in tryptase ■ tryptase decreased to <20 ng/mL</p> ■ tryptase normalized to <11.4 ng/mL</p> *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 treatment⁶
- Results from the EXPLORER study led to the initiation of the phase 2, randomized, double-blind, placebocontrolled 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

Key Eligibility Criteria

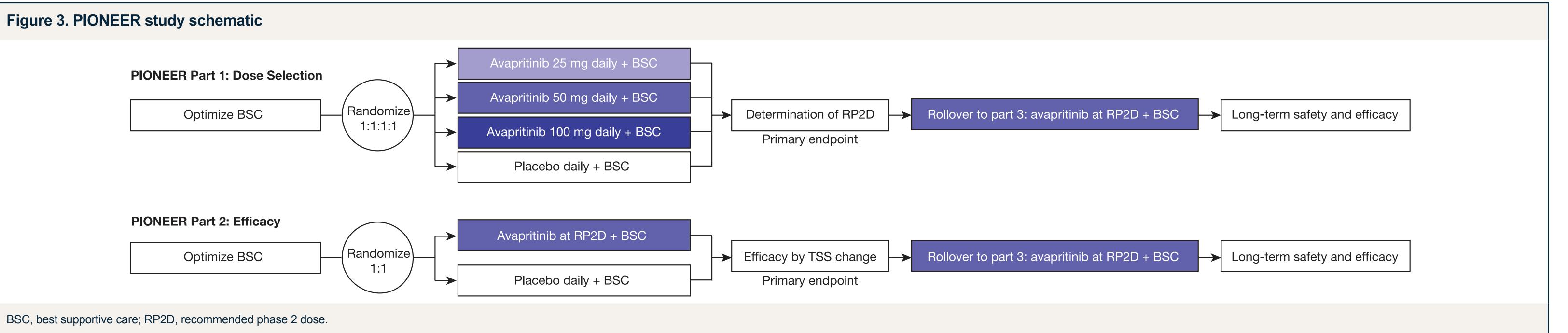
- Age ≥18 years
- Eastern Cooperative Oncology Group performance status 0–2

safety and efficacy of avapritinib (part 3; rollover)

- 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.



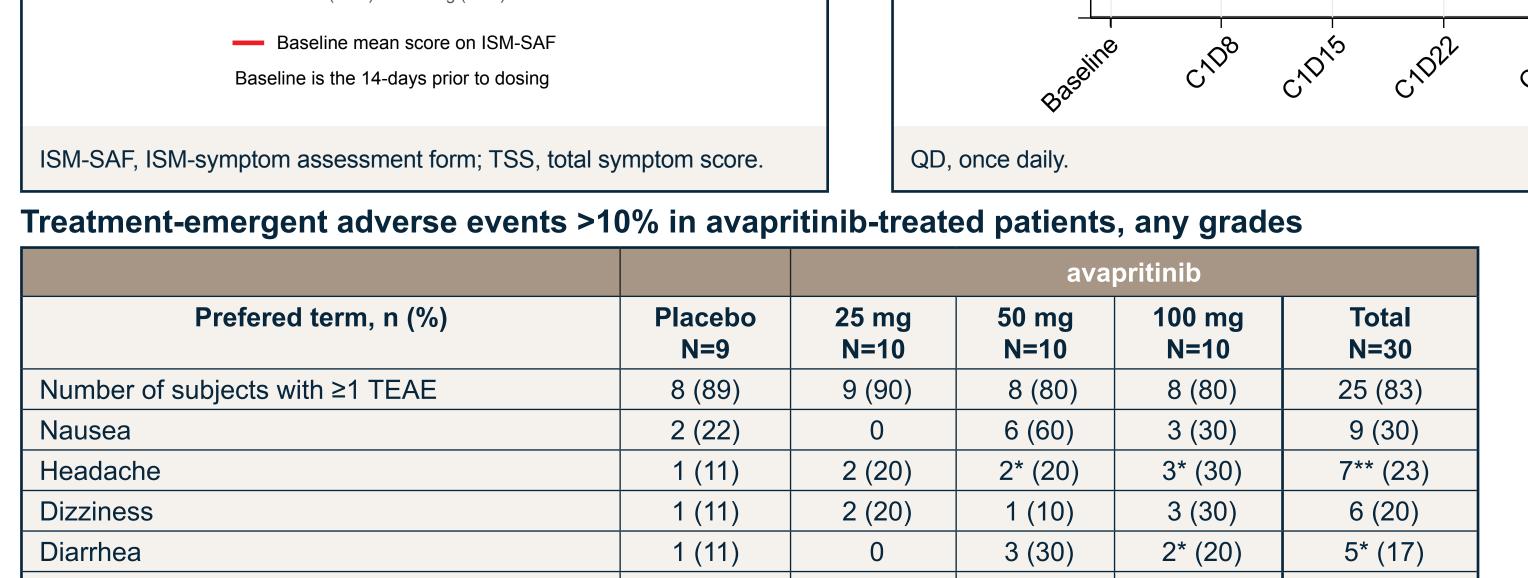
RESULTS

Data cutoff date: November 12, 2019 erum tryptase levels over time by dose

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

Figure 4. Mean symptom scores at baseline	Figure 5. Mean se	
Fatigue (100% of patients reported baseline fatigue) Brain fog (100%) Nausea (95%) Dizziness (92%) Dizziness (92%) Bone pain (92%)	Mean % change in serum tryptase 6 - 4 - 6 - 6 - 6	ser
Headache (97%) Itching (92%) — Baseline mean score on ISM-SAF	-80	
Baseline is the 14-days prior to dosing	Baseline	
ISM-SAF, ISM-symptom assessment form; TSS, total symptom score.	QD, once daily.	



3 (30)

- *Includes 1 ≥grade 3 event. **Includes 2 ≥grade 3 events across all avapritinib doses Note: Cognitive disorder occured 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. AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Prefered term, n (%)

Number of subjects with ≥1 TEAE

Headache

Dizziness

Face edema

Diarrhea

Most severe baseline symptoms are fatigue, brain fog,

avapritinib 25 mg QD

avapritinib 100 mg QD

avapritinib 50 mg QD

- 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
- 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 avapritinibtreated 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 PIONEER Ø Location **Indolent & Smoldering SI** 1 Dana-Farber Cancer Institute Active Site 2 University of Utah Planned Site Stanford Hospital & Clinics - Stanford Columbia University Medical Center - HICCC New York, NY University of Michigan Brigham and Women's Hospital St. Michaels's Hospital Toronto, Canada Location Guy's and St Thomas' NHS Foundation Trust – St. Thomas' Hospital University Medical Center Groningen Groningen, Netherlands Azienda Ospedaliera Universitaria San Giovanni di Dio e Ruggi d'Aragona Salerno, Italy Jniversity Medical Centre Mannheim Mannheim, Germany echnical University Munich, Department of Dermatology Biederste 14 University Hospital Aachen Aachen, Germany 15 Odense University Hospital Odense, Denmark

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

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QR Code Disclaimer

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Avapritinib is an investigational agent discovered by and currently in development by Blueprint



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Lübeck, Germany

Berlin, Germany

Mainz, Germany

Edegem, Belgium

Basel, Switzerland

Performance Status: MC. mast cell: SD. standard deviation