Avapritinib Induces Responses in Patients with Advanced Systemic Mastocytosis (AdvSM), Regardless of Prior Midostaurin Therapy

EP1079

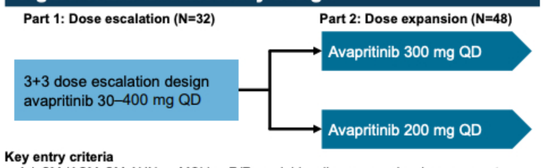
Jason Gotlib,[1] Deepti H. Radia,[2] Tracy I. George,[3] William A. Robinson,[4] Albert T. Query,[5] Mark W. Drummond,[6] Prithviraj Bose,[7] Elizabeth O. Hexner,[8] Elliott F. Winton,[9] Hans-Peter Horny,[10] Meera Tugnait,[11] Oleg Schmidt-Kittler,[11] Erica K. Evans,[11] Hui-Min Lin,[11] Brenton G. Mar,[11] Michael W. Deininger,[12] Daniel J. DeAngelo[13]

[1]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA; [2]Guy's and St Thomas' NHS Foundation, London, UK; [3]ARUP Laboratories, University of Utah, Salt Lake City, UT, USA; [4]UC Anschutz Medical Campus, Aurora, CO, USA; [5]University of Michigan, Ann Arbor, MI, USA; [6]Beatson Cancer Centre, Glasgow, UK; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [9]Winship Cancer Institute of Emory, University Atlanta, Atlanta, GA, USA; [10]Institute of Pathology, Ludwig-Maximilians University, Munich, Germany; [11]Blueprint Medicines Corporation, Cambridge, MA, USA; [12]Division of Hematology and Hematologic Malignancies, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA; [13] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Background and methods

- Systemic mastocytosis (SM) is a **clonal mast cell (MC) neoplasm driven by the *KIT* D816V mutation** characterised by severe skin, gastrointestinal and systemic MC mediator symptoms[1,2]
- In addition to MC activation symptoms, patients with **AdvSM have poor overall survival (OS),** with median OS ≤3.5 years, due to organ damage and/or severe pathologic features[3–5]
- AdvSM comprises three subtypes: aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), and MC leukemia (MCL)[4]
- Midostaurin, a multikinase inhibitor, is approved for AdvSM; however, few patients achieve complete remissions, and patients commonly experience gastrointestinal adverse events (e.g. vomiting and nausea), which contribute to high rates of discontinuation[5,6]
- Avapritinib is a selective and potent inhibitor of KIT D816V[7]
- EXPLORER (NCT02561988, Figure 1) is an ongoing phase 1 study designed to determine the recommended phase 2 dose (RP2D), safety and preliminary efficacy of avapritinib in patients with AdvSM and relapsed/refractory myeloid malignancies
- **Cut-off date for presented data:** 30 August 2019

Figure 1: EXPLORER study design



Key entry criteria
- AdvSM (ASM, SM-AHN, or MCL) or R/R myeloid malignancy per local assessment
- Age ≥18 years, ECOG PS 0–3, platelets ≥50 x 10^9/L

Study objectives
- Primary: RP2D and safety
- Secondary: antineoplastic activity, pharmacokinetics, changes in serum tryptase and blood/bone marrow *KIT* D816V mutant allele fraction, and patient-reported outcomes

ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; R/R, relapsed/refractory.

Results

Table 1: Baseline characteristics

Characteristic	mIWG evaluable (n=48)	All patients (N=80)
Median age (range), years	66 (34–83)	64 (34–83)
Male, n (%)	28 (58)	42 (53)
ECOG PS, n (%)		
0–1	32 (67)	59 (74)
2–3	16 (33)	21 (26)
Any prior anti-neoplastic therapy, n (%)	30 (63)	51 (64)
Midostaurin	15 (31)	24 (30)
Cladribine	7 (15)	13 (16)
SM subtype by central assessment, n (%)		
AdvSM	48 (100)	62 (78)
ASM	3 (6)	7 (9)
SM-AHN	35 (73)	44 (55)
MCL	10 (21)	11 (14)
Other*	0	18 (23)
***KIT* mutation by central assays, n (%)**		
D816V positive by ddPCR	46 (96)	73 (91)
D816Y positive by NGS	2 (4)	2 (3)
Negative for D816 mutation	0	5 (6)
***SRSF2/ASXL1/RUNX1* positive, n (%)**	26 (54)	36 (45)
Median BM MC burden (range), %	50 (5–95)	30 (5–95)
Median serum tryptase (range), ng/mL	178 (21–765)	158 (12–1414)
Median *KIT* D816V allele burden (range), %	17 (0–81)	10 (0–81)
Median spleen volume (range), mL	1175 (258–2300)	827 (130–2300)

*Fourteen patients with indolent SM, two with smoldering SM and one with chronic myelomonocytic leukemia; one patient's diagnosis was pending central adjudication. BM, bone marrow; ddPCR, droplet digital polymerase chain reaction; mIWG evaluable, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis evaluable; NGS, next-generation sequencing.

Table 2: Best ORR (mIWG-MRT-ECNM)

- High overall response rate (ORR) was achieved across all AdvSM subtypes with responses (confirmed) in both midostaurin-naïve and midostaurin-treated patients
- Reasons for discontinuing midostaurin therapy included disease progression/relapse (33%), adverse events (33%), inadequate response (17%), and unknown/other (17%)

Best response	All evaluable (n=48)	By AdvSM subtype: ASM (n=3)	SM-AHN (n=35)	MCL (n=10)	By prior therapy: Prior mido Yes (n=15)	No (n=33)
ORR, % (95% CIs)	77 (63–88)	**100**	77	70	**60**	85
CR+CRh, n (%)	13 (27)	**2 (67)**	9 (26)	2 (20)	**0**	13 (39)
CR, n (%)	4 (8)	**0**	2 (6)	2 (20)	**0**	4 (12)
CRh, n (%)	9 (19)	**2 (67)**	7 (20)	0	**0**	9 (27)
PR, n (%)	20 (42)	**1 (33)**	16 (46)	3 (30)	**8 (53)**	12 (36)
CI, n (%)	4 (8)	**0**	2 (6)	2 (20)	**1 (7)**	3 (9)
SD, n (%)	10 (21)	**0**	7 (20)	3 (30)	**5 (33)**	5 (15)
PD, n (%)	0	**0**	0	0	**0**	0
NE, n (%)	1 (2)	**0**	1 (3)	0	**1 (7)**	0

CI, clinical improvement; CIs, confidence intervals; CR, complete remission; CRh, complete remission with partial haematologic recovery; Mido, midostaurin; NE, not evaluable; PD, progressive disease; PR, partial remission; SD, stable disease.

Figure 2: Patient-reported outcomes

- Patients in Part 2 participated in patient-reported outcome collection with the AdvSM-Symptom Assessment Form (SAF)
- The severity of eight symptoms was queried daily and summed as a Total Symptom Score (TSS; range: 0–80)
- Mean TSS at baseline was 18.7 points (n=33)

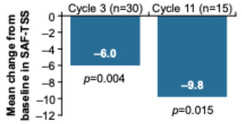
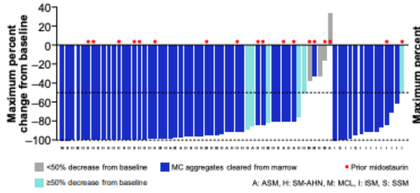
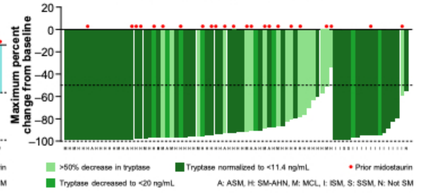


Figure 3: Change in measures of MC burden

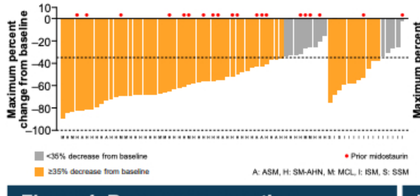
Bone marrow MCs
Marrow MC aggregates were decreased by ≥50% in 93% of patients, and eliminated in 85% of patients



Serum tryptase
99% of patients had ≥50% reduction in serum tryptase and in 67% serum tryptase normalised



Spleen volume
Spleen volume was reduced by ≥35% in 80% of patients, and in 81% of patients who had palpable spleen at baseline spleen became non-palpable



***KIT* D816V mutation allele fraction**
KIT D816V allele fraction decreased by ≥50% in 92% of patients, and to <1% in 68% of patients

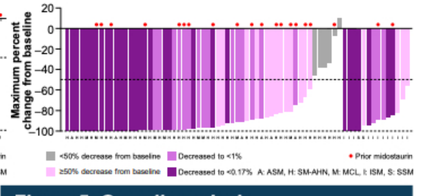


Figure 4: Responses over time

- Median time to initial confirmed response was ~2 cycles
- Responses deepen over time into complete responses
- 3-year duration of response was 63% (95% CI, 39–88%)

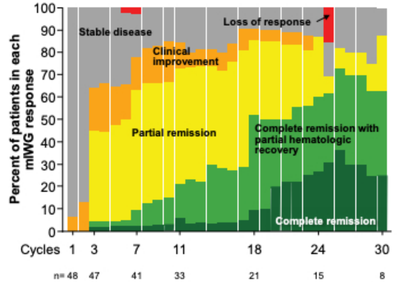


Figure 5: Overall survival

- Median OS at 24 months was not reached for any subtype
- OS profile was not significantly different between patients who received prior midostaurin and those who did not

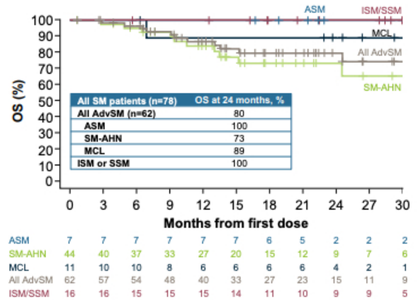


Table 3: Adverse events (AEs, N=80)

Event	All grades	Grade ≥3
Non-hematologic AEs in ≥20% of patients, n (%)		
Periorbital oedema	57 (71)	3 (4)
Diarrhoea	33 (41)	1 (1)
Fatigue	32 (40)	7 (9)
Peripheral oedema	32 (40)	0
Nausea	31 (39)	3 (4)
Vomiting	27 (34)	3 (4)
Cognitive effect*	27 (34)	3 (4)
Hair colour change	22 (28)	1 (1)
Arthralgia	20 (25)	1 (1)
Abdominal pain	17 (21)	1 (1)
Constipation	17 (21)	1 (1)
Dizziness	16 (20)	1 (1)
Hematologic AEs in ≥10% of patients, n (%)		
Anaemia	44 (55)	23 (29)
Thrombocytopaenia	31 (39)	21 (26)
Neutropenia	11 (14)	10 (13)

*Cognitive effects include the following AE terms: cognitive disorder, confusional state and memory impairment.

- Most of AEs were Grade 1 and 2; 15% (12/80) of patients discontinued treatment due to clinical progression and 8% (6/80) due to treatment-related AEs
- Non-traumatic intracranial bleeding (ICB) occurred in 8% (6/80) of patients, 4 were asymptomatic; an additional patient experienced ICB event, which was considered related to a severe fall
- Among patients with platelets <50,000/µL at baseline, 44% (4/9) had an ICB event, while in patients with platelets ≥50,000/µL at baseline, 3% (2/71) had an non-traumatic ICB event, both asymptomatic and associated with treatment-emergent severe thrombocytopenia (<50,000/µL)
- Severe thrombocytopenia now managed by strict dose interruption/reduction and platelet support

Conclusions

- Avapritinib induced rapid, deep and durable reductions in measures of MC burden, which were associated with significant reduction in disease-related symptoms regardless of prior midostaurin exposure or AdvSM subtype
- The starting dose of avapritinib in patients with AdvSM is 200 mg QD
- In patients with platelets ≥50,000/µL, ICB events were uncommon
- The phase 2 PATHFINDER trial is currently enrolling patients with AdvSM to further characterize the safety and efficacy of avapritinib

References

1. Gulen T et al. *J Intern Med.* 2016;279:211–228; 2. Pardanani A. *Am J Hematol.* 2016;91:1146–1159; 3. Lim K-H et al. *Blood.* 2009;113:5727–5736; 4. Gotlib J et al. *Blood.* 2013;121:2392–2401; 5. Gilreath JA et al. *Clin Pharmacol.* 2019;11:77–92; 6. Gotlib J et al. *N Engl J Med.* 2016;374:2530–2541; 7. Evans EK et al. *Sci Transl Med.* 2017;9:414.

Acknowledgements

The authors would like to thank the patients, their families and all investigators involved in this study. Medical writing support was provided by Miriam Cohen, PhD, and editorial support was provided by Elke Sims, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, USA, according to Good Publication Practice guidelines.

Disclosures

Study sponsored by Blueprint Medicines Corporation. JG is the Chair of the Response Adjudication Committee, received research funding, served on advisory boards, and received honoraria and funding to cover travel expenses from Blueprint Medicines Corporation. DR, WAR, PB, EOH, MT, OSK and EKE received research funding from Blueprint Medicines Corporation. EW received research funding from Blueprint Medicines Corporation, Samus Therapeutics and Incyte Corporation. TIG, received consulting fees from Blueprint Medicines Corporation. HPH, served as a consultant for Novartis and Blueprint Medicines Corporation. HML and BGM are employees of and own stocks or other ownerships in Blueprint Medicines Corporation. DHD served as a consultant for Amgen, Autolus, Agios, Blueprint Medicines Corporation, Forty-Seven, Incyte Corporation, Jazz, Novartis, Pfizer, Shire, and Takeda, and received research funding from Abbvie, Glycomimetics, Novartis and Blueprint Medicines Corporation. ATQ has nothing to declare.

Presented at the **25th European Hematology Association Congress 2020,** 11–14 June 2020, virtual format. Please contact medinfo@blueprintmedicines.com for permission to reprint and/or distribute