Avapritinib (BLU-285), a Selective KIT Inhibitor, is Associated with High Response Rate and Tolerable Safety Profile in Advanced Systemic Mastocytosis: Results of a Phase 1 Study

Michael W. Deininger[1], Jason Gotlib[2], William A. Robinson[3], Deepti H. Radia[4], Mark W. Drummond[5], Albert T. Quiery[6], Elizabeth Hexner[7], Srdan Verstovsek[8], Hongliang Shi[9], Oleg Schmidt-Kittler[9], Meera Tugnait[9], Maureen G. Conlan[9], Daniel J. DeAngelo[10].

[1]University of Utah, Salt Lake City, USA; [2]Stanford Cancer Institute/Stanford University School of Medicine, Stanford, USA; [3]University of Colorado Denver, Aurora, USA; [4]Guys and St Thomas NHS Foundation, London, UK; [5]Beatson Cancer Centre, Glasgow, UK; [6]University of Michigan, Ann Arbor, USA; [7]University of Pennsylvania, Philadelphia, USA; [8]University of Texas MD Anderson Cancer Center, Houston, USA; [9]Blueprint Medicines Corporation, Cambridge, USA; [10]Dana-Farber Cancer Institute, Boston, Massachusetts, USA.

Background

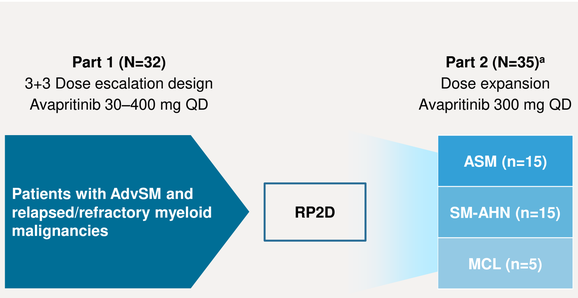
- Systemic mastocytosis (SM) encompasses a spectrum of mast cell disorders characterized by an accumulation of neoplastic mast cells in tissues/visceral organs[1,2]
- Constitutively active mutant KIT (typically D816V) is present in 90–95% of SM cases and is central to disease pathogenesis[3–5]
- Advanced systemic mastocytosis (AdvSM) is the most severe form of SM comprising three subtypes, aggressive SM (ASM), SM with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL),[1,2] classified using the World Health Organization (WHO) diagnostic criteria[5,6]
- The multi-kinase inhibitor midostaurin is currently the only approved treatment for all subtypes of AdvSM, but is not optimized for selective KIT D816V inhibition[7,8]
- Avapritinib is a highly potent and selective kinase inhibitor, developed to specifically target the active conformation of KIT, conferring potent and selective inhibition of KIT D816V and other activation loop mutants[9]

Methods

Study design and assessments

- EXPLORER is a two part, Phase 1, multicenter study of avapritinib in adult patients with AdvSM or relapsed/refractory myeloid malignancies (**Figure 1, Table 1**)

Figure 1. Study design



- **Primary objectives:** MTD/RP2D and safety profile
- **Secondary objectives**: Preliminary antineoplastic activity and PK

ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended Phase 2 dose; SM AHN, systemic mastocytosis with associated hematologic neoplasm
[a] As of 30 April 2018, 20 patients have been enrolled in Part 2

- **Antineoplastic activity was assessed by:** Changes in percentage of bone marrow mast cells, splenomegaly, serum tryptase, KIT D816V mutant allele burden
  - Overall response assessed by modified International Working Group Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis criteria (m-IWG-MRT-ECNM)
    - C-findings per m-IWG-MRT-ECNM criteria necessary for response assessment
    - Complete response (CR) with partial recovery of peripheral blood counts (CRh) added to accommodate CR with residual cytopenias due to avapritinib
    - Response is confirmed 12 weeks after first documentation of response
    - Response adjudicated by a Response Adjudication Committee (RAC), composed of subset of study investigators

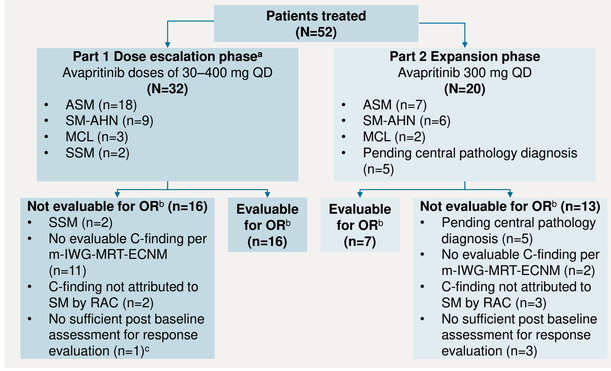
Table 1. Patient population

Key inclusion criteria	Key exclusion criteria
Diagnosis of AdvSM (ASM, SM-AHN or MCL) per WHO criteria or a relapsed/refractory myeloid malignancy	Diagnosis of acute myeloid leukemia
≥1 "C-finding" based on WHO criteria for diagnosis of ASM and SM-AHN	High-risk myelodysplastic syndrome or Philadelphia chromosome positive malignancy
Age ≥18 years	Brain metastases or risk for CNS hemorrhage
ECOG performance score (PS) of 0–3	

Results

- As of 30 April 2018, a total of 52 patients received avapritinib; 32 in Part 1 and 20 in Part 2 (**Figure 2**)
- Median duration of treatment was 14 months (range 1-26 months) in Part 1 and 5 months (range 1-9 months) in Part 2; 42 (80%) patients remain on treatment
- Baseline demographics and disease characteristics for all 52 patients are shown in **Table 2**

Figure 2. Patient disposition



OR, overall response; RAC, Response Adjudication Committee; SSM, smoldering systemic mastocytosis; WT, wild-type.
[a] Additional accrual was allowed to dose levels declared safe;[b] Based on m-IWG-MRT-ECNM criteria;
[c] *KIT* wild type, discontinued prior to post baseline response assessment

Table 2. Patient demographics and disease characteristics

Characteristic, n (%)	Part 1 (N=32)	Part 2 (N=20)	All patients (N=52)
Age (years), median (range)	63 (34, 83)	62 (40, 77)	63 (34, 83)
Gender, male	16 (50)	11 (55)	27 (52)
Prior cytoreductive therapy	20 (69)	13 (65)	35 (67)
Number of prior cytoreductive therapies			
0	10 (31)	7 (35)	17 (33)
1	13 (41)	9 (45)	22 (42)
2	7 (22)	2 (10)	9 (17)
3	2 (6)	2 (10)	4 (8)
ECOG PS			
0	7 (22)	6 (30)	13 (25)
1–2	25 (78)	10 (50)	35 (67)
3	0	4 (20)	4 (8)
***KIT* Exon 17 mutation status[a]**			
D816V	28 (88)	17 (85)	45 (87)
D816Y	1 (3)	0	1 (2)
Wild-type	3 (9)	3 (15)	6 (12)
Bone marrow MC burden (% MC)[b], median (range)	20 (1.5, 95.0)	50 (10.0, 95.0)	25 (1.5, 95.0)
Serum tryptase (µg/L), median (range)	124 (14, 1414)	216 (13, 491)	161 (13, 1414)
Spleen volume (mL)[c], median (range)	626 (130, 1952)	1064 (359, 1923)	685 (130, 1952)
KIT D816V mutant allele burden (%)[d], median (range)	4.48 (0.09, 47.30)	23.45 (0.16, 80.10)	11.52 (0.09, 80.10)
Mastocytosis in the skin	14 (44)	9 (45)	23 (44)

ECOG PS, Eastern Cooperative Oncology Group performance score; MC, mast cell; [a] Based on local testing;
[b] Results for Part 1 patients are based on local assessment, results for Part 2 patients are based on central pathology review (N=45);
[c] Spleen volume assessed by Central Radiology Review (N=48); [d] Mutation allele burden (%) assessed by Central Laboratory; (MolecularMD) using a validated c-KIT D816V ddPCR assay with limit of detection of 0.13% mutant allele fraction (N=42)

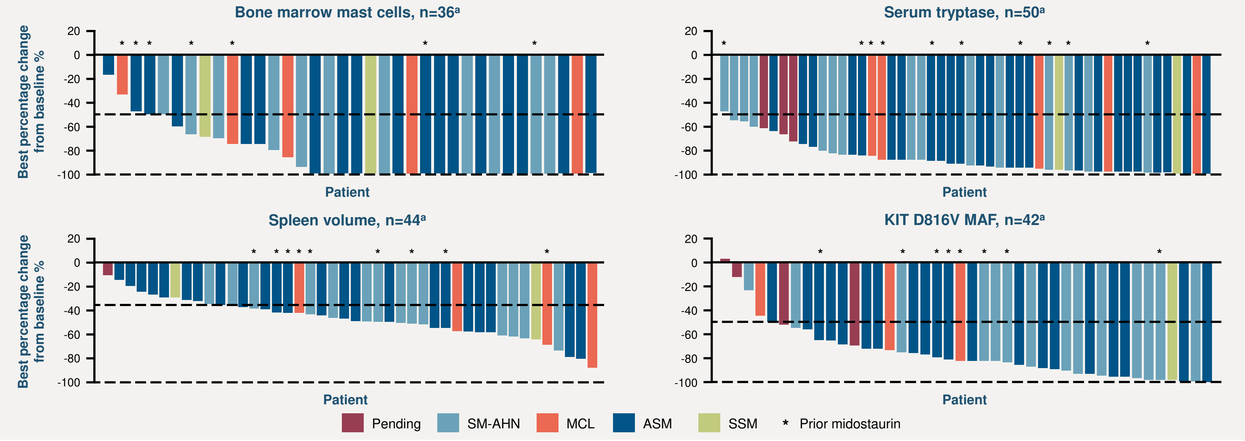
Antineoplastic activity

Table 3. Antineoplastic activity: changes in measures of mast cell burden

Best Response, n (%)	Part 1 (N=32)	Part 2 (N=20)	All patients (N=52)
Bone marrow MCs	**27**	**9**	**36**
No neoplastic MCs present	16 (59)	5 (56)	21 (58)
≥50% decrease in neoplastic MCs[a]	8 (30)	4 (44)	12 (33)
<50% decrease in neoplastic MCs	3 (11)	0	3 (8)
Serum tryptase[b]	**32**	**18**	**50**
<20 µg/L	24 (75)	9 (50)	33 (66)
≥50% decrease	8 (25)	8 (44)	16 (32)
<50% decrease	0	1 (6)	1 (2)
Splenomegaly[c]	**11**	**8**	**19**
Normal spleen length by imaging or nonpalpable	6 (55)	3 (38)	9 (47)
≥35% decrease in spleen volume by imaging or ≥50% reduction by palpation	5 (45)	4 (50)	9 (47)
<35% decrease in spleen size by imaging or <50% reduction by palpation	0	1 (13)	1 (5)
KIT D816V mutant allele burden in bone marrow[d]	**26**	**16**	**42**
≥50% decrease	23 (88)	14 (88)	37 (88)
<50% decrease	3 (12)	1 (6)	4 (10)
Increase	0	1 (6)	1 (2)
Mastocytosis in the skin	**14**	**9**	**23**
Improvement based on Investigator assessment	13 (93)	7 (78)	20 (87)

MC, mast cells; [a] Only applies if baseline BM MCs are ≥5%; [b] Assessed by Central Laboratory; [c] Only applies if baseline spleen is ≥5 cm by palpation; [d] Assessed by Central Laboratory. In Part 1: 3 patients have wild type *KIT*, 3 patients have *KIT* mutation that is not D816V (2 D816Y and 1 M541L). In Part 2: 3 patients have wild type *KIT*, and 1 patient has no post-baseline assessment result as of 30 April 2018

Figure 3. Change in bone marrow mast cells, serum tryptase, spleen volume and KIT D816V MAF



MAF, mutant allele fraction; [a] number of patients evaluable for each parameters

Table 4. Best overall response per m-IWG-MRT-ECNM criteria

	Part 1 (Best confirmed response)				Part 2 (Best unconfirmed response)[a]				Part 1 and 2
Response, n (%)	ASM (n=7)	SM-AHN (n=6)	MCL (n=3)	All (n=16)	ASM (n=1)	SM-AHN (n=4)	MCL (n=2)	All (n=7)	All (n=23)
ORR (CR/CRh + PR + CI)	6 (86)	4 (67)	3 (100)	**13 (81)**	1 (100)	3 (75)	2 (100)	**6 (86)**	**19 (83)**
Clinical Benefit Rate (CR/CRh + PR + CI + SD)	7 (100)	6 (100)	3 (100)	**16 (100)**	1 (100)	4 (100)	2 (100)	**7 (100)**	**23 (100)**
CR/CRh + PR	5 (71)	4 (67)	2 (67)	**11 (69)**	1 (100)	2 (50)	2 (100)	**5 (71)**	**16 (70)**
CR/CRh	4 (57)	0	0	**4 (25)**	0	0	0	**0**	**4 (17)**
CR	1 (14)	0	0	**1 (6)**	0	0	0	**0**	**1 (4)**
CRh	3 (43)	0	0	**3 (19)**	0	0	0	**0**	**3 (13)**
PD	0	0	0	**0**	0	0	0	**0**	**0**

ORR, overall response rate; CI, clinical improvement; PR, partial response; SD, stable disease; clinical improvement; PD, progressive disease; [a] pending 12 week confirmation

Overall response rate per modified IWG-MRT-ECNM criteria

- In Part 1 and Part 2 of the study, 16 and 7 patients, respectively, were evaluable for response per m-IWG-MRT-ECNM criteria. Response data are presented in **Table 4**
- In Part 1, all responses were confirmed at 12 weeks
  - Time to response was rapid, with most patients (11/13, 85%) experiencing first evidence of response at the start of Cycle 3; median time to first resolution of at least one evaluable C-finding was 35 days
  - Duration of response ranged from 8 to 22 months
- In Part 2, all responses were unconfirmed (pending 12 week confirmation)
- 15/19 (79%) responding patients remain on treatment

Reduction in mast cell burden

- In both Part 1 and Part 2, a high rate of response was observed for each measure of mast cell burden (**Figure 3, Table 3**); this was consistent across all subtypes of AdvSM
- Among 36 patients with bone marrow mast cells ≥5% and post baseline bone marrow assessment and tryptase measurement, 29 (81%) had ≥ 50% reduction in both parameters.

Safety

- 50 patients (96%) reported an adverse event (AE) occurring at any grade (**Table 5**); Grade ≥3 treatment-related AEs were reported in 28 (54%) patients
- Other AEs of interest include: ascites (n=5 [10%]; n=2 [4%] at ≥Grade 3) and pleural effusion (n=5 [10%]; n=0 at ≥Grade 3)
- Dose reductions and interruptions due to AEs were reported in 29 (56%) patients each, most of which occurred at doses >200 mg QD
- Ten patients discontinued from study treatment: n=4, AE (Grade 4 related refractory ascites; Grade 5 unrelated sepsis; Grade 2 related encephalopathy; Grade 2 related confusional state); n=3 clinical progression (not meeting criteria for PD per m-IWG-MRT-ECNM criteria), n=2, investigator's decision, n=1 withdrawal of consent

Table 5. Adverse events reported in ≥20% of patients (N=52)

	AEs regardless of study drug relationship				Any grade treatment-related
AE, n (%)	Any grade	Grade 1	Grade 2	Grade ≥3	
Non-hematological					
Periorbital edema	32 (62)	22 (42)	8 (15)	2 (4)	32 (62)
Fatigue	21 (40)	9 (17)	9 (17)	3 (6)	16 (31)
Nausea	19 (37)	10 (19)	7 (13)	2 (4)	17 (33)
Diarrhea	18 (35)	10 (19)	6 (12)	1 (2)	13 (25)
Peripheral edema	18 (35)	14 (27)	3 (6)	0	14 (27)
Cognitive effects[a]	13 (25)	8 (15)	4 (8)	1 (2)	10 (19)
Vomiting	13 (25)	7 (13)	3 (6)	3 (6)	10 (19)
Hair color changes	12 (23)	11 (21)	0	1 (2)	12 (23)
Dizziness	11 (21)	9 (17)	2 (4)	0	6 (12)
Hematological					
Anemia	22 (42)	6 (12)	8 (15)	8 (15)	17 (33)
Thrombocytopenia	16 (31)	5 (10)	2 (4)	9 (17)	10 (19)

[a] Cognitive effects include the following AE terms: cognitive disorder, confusional state, and memory impairment

Conclusions

- Avapritinib has potent antineoplastic activity across all subtypes of AdvSM, with an ORR of 83% per m-IWG-MRT-ECNM criteria, and responses were durable
- Avapritinib treatment resulted in deep and durable reductions in levels of bone marrow mast cells, serum tryptase, splenomegaly and KIT D816V mutant allele burden, as well as reversal of organ damage, in all subtypes of AdvSM, regardless of prior treatment
- 50% or greater reduction in both BM mast cells and tryptase occurred in 81% of patients, including those not evaluable for response by m-IWG-MRT-ECNM criteria
- Avapritinib was well-tolerated, and the majority of patients remain on study treatment
- Expansion (Part 2) is ongoing and Phase 2 PATHFINDER study is planned to start enrollment by the middle of 2018 to further investigate efficacy and tolerability of avapritinib in AdvSM
- Data support further evaluation of avapritinib across the spectrum of SM, including indolent SM and smoldering SM; a Phase 2 clinical study (PIONEER) is planned to start in these indications by the end of 2018

References

1. Lim K-H et al. Blood 2009;113:5727-36.
2. Gulen T et al. J Intern Med 2016;279:211-28.
3. Kristensen T et al. The Journal of molecular diagnostics. 2011;13:180-8.
4. Garcia-Montero AC et al. Blood 2006;108:2366-72.
5. Pardanani A. Am J Hematol 2016;91:1146-59.
6. Gotlib J et al. Blood 2013;121:2393-401.
7. Gotlib J et al. N Engl J Med 2016;374:2530-41.
8. FDA. RYDAPT (midostaurin) Highlights of Prescribing Information. 2017.
9. Evans et al. Sci Transl Med. 2017;9(414):eaao1690.

Acknowledgments

- We thank the participating patients, their families, all study co-investigators, research coordinators and data managers who contributed to this study
- We thank Sarah Jackson from iMed Comms an Ashfield Company, part of UDG Healthcare plc, who provided medical writing support funded by Blueprint Medicines

EXPLORER Advanced SM