Avapritinib in the Post-allogeneic Hematopoietic Stem Cell Transplant Setting in Patients With Advanced Systemic Mastocytosis

Poster Number: P262

Poster available for download at

Deborah Christen,[1,2] Johannes Lübke,[3] Juliana Schwaab,[3] Anne Kaiser,[1,2] Svetlana Rylova,[4] Saša Dimitrijević,[4] Ilda Bidollari,[5] Jens Peter Panse,[1,2] Andreas Reiter[3]

[1]Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation, University Hospital RWTH Aachen, Aachen, Germany, [2]Center for Integrated Oncology Aachen, Bonn, Cologne, Düsseldorf (CIO ABCD), Aachen, Germany, [3]Department of Hematology and Oncology, University Hospital Mannheim, Heidelberg University, Mannheim, Germany, [4]Blueprint Medicines (Switzerland) GmbH, Zug, Switzerland, [5]Blueprint Medicines, Cambridge, MA, USA

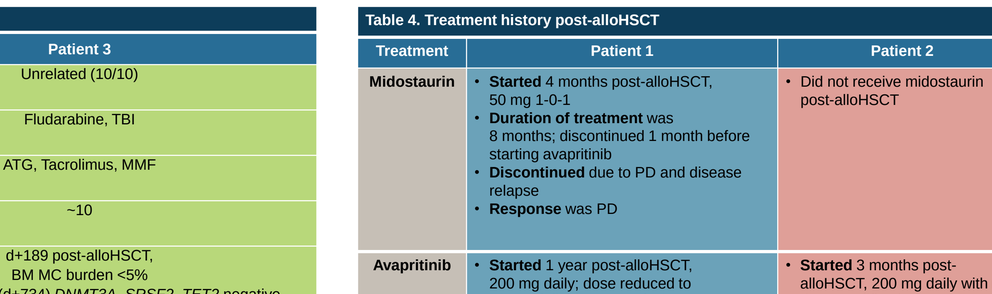
Background

- Advanced Systemic Mastocytosis (AdvSM) is a rare clonal hematologic neoplasm associated with poor survival and driven by *KIT* D816V mutation in ~95% of cases[1-3]
- Avapritinib, a highly potent and selective tyrosine kinase inhibitor targeting *KIT* D816V, significantly improved outcomes for patients with AdvSM in the EXPLORER and PATHFINDER studies by inducing deep and durable responses[3,4]
  - Avapritinib is not recommended in patients with AdvSM with platelet counts <50 × 10^9/L due to risk of intracranial bleeding[5]
- Allogeneic hematopoietic stem cell transplantation (alloHSCT) has been used to treat AdvSM, but its definitive role is unclear; outcomes of alloHSCT in AdvSM may be dependent upon the disease phenotype and response to treatment prior to alloHSCT[6-8]
- Use of avapritinib to induce remission prior to alloHSCT in AdvSM was reported previously[9]
- However, little is known about the role of avapritinib in the post-alloHSCT setting of AdvSM
- We here describe first experiences with avapritinib post-alloHSCT in patients with AdvSM enrolled in the PATHFINDER study

Methods

- PATHFINDER is an international, multicenter, open-label, single-arm, phase 2 registrational trial (**Figure 1**)

Figure 1. Study design



[a]Two patients initiated 100 mg QD avapritinib, all others initiated at 200 mg QD. [b]Disease burden measures include BM MCs, serum tryptase, *KIT* D816V VAF, and spleen volume.
AML, acute myeloid leukemia; BM, bone marrow; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; MC, mast cell; MDS, myelodysplasia syndrome; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; VAF, variant allele fraction; WHO, World Health Organization.

- Hospital records of all patients enrolled in PATHFINDER were retrospectively reviewed to identify those who received avapritinib post-alloHSCT
- *KIT* D816V variant allele fraction (VAF), tryptase levels, and alkaline phosphatase levels were assessed in peripheral blood
- Mast cell burden was assessed in bone marrow
- Responses to treatment were assessed centrally using modified International Working Group-Myeloproliferative Neoplasms Research and Treatment and European Competence Network on Mastocytosis (mIWG-MRT-ECNM) criteria[2]
- Treatment journeys for each patient are depicted above each graph

Results

Table 1. Demographics and clinical characteristics

	Patient 1	Patient 2	Patient 3	Summary
Sex	Male	Male	Male	All were male, aged 61-68 years, with diagnosis of mast cell leukemia with associated hematologic neoplasm. All had normal cytogenetics, and Sorror score was 0 (patients 1 and 3) or 5 (patient 2)
Age, years	68	61	64	
Diagnosis	MCL-ET	MCL-MDS IB1	MCL-MDS/MPN, NOS	
Cytogenetics	Normal	Normal	Normal	
ECOG PS	0	1	0	
Karnofsky PS index	100%	90%	90%	
Sorror score[10]	0	5	0	
B findings	Splenomegaly	Splenomegaly, BM MC burden >30%	None	
C findings	Ascites	None	BM dysfunction with platelets <100 g/L, GI involvement with weight loss, palpable splenomegaly with hypersplenism	
BM MC %	10	50	90	
Basal serum tryptase, µg/L	23.8	146.0	624.0	
***KIT* D816V VAF, %**	0.01	0.08	12.58	
S/A/R mutations	none	none	*SRSF2*	

BM, bone marrow; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ET, essential thrombocytopenia; MC, mast cell; MCL, mast cell leukemia, MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NOS, not otherwise specified; PS, performance status; S/A/R, *SRSF2*, *ASXL1*, *RUNX1*; VAF, variant allele frequency.

Table 2. Treatment history prior to alloHSCT

Treatment	Patient 1	Patient 2	Patient 3	Summary
Midostaurin	• **Duration of treatment** ~10 months • **Best response** was SD • **Discontinued** due to PD	• **Duration of treatment** ~8 months • **Best response** was PD • **Discontinued** due to progressive anemia	• **Duration of treatment** ~2.5 months; discontinued 1 month prior to starting avapritinib • **Best response** was PD • **Discontinued** due to neutropenia	• All patients received midostaurin prior to alloHSCT • All discontinued midostaurin due to lack of response or toxicity
Avapritinib	• Did not receive avapritinib prior to alloHSCT	• Did not receive avapritinib prior to alloHSCT	• Entered PATHFINDER • **Started** avapritinib 200 mg daily; dose was reduced to 50 mg then 25 mg daily over the next month due to thrombocytopenia and neutropenia. After ~7 weeks at 25 mg, the dose was escalated to 50 mg and then 100 mg daily • **Duration of treatment w**as 1 year, 6 months • **Best response** was CI: *KIT* D816V VAF decreased from 12.58% at baseline to 4.55%; bone marrow MC infiltration decreased from 90% at baseline to 10%	

CI, clinical improvement; MC, mast cell; PD, progression of disease; SD, stable disease; VAF, variant allele fraction.

Table 3. Donor and alloHSCT characteristics

	Patient 1	Patient 2	Patient 3
Type of donor (match)	Unrelated (10/10) PS, performance status;	Related (10/10)	Unrelated (10/10)
Conditioning	Fludarabine, Busulfan	Fludarabine, Treosulfan	Fludarabine, TBI
GVHD prophylaxis	CsA, MTX, ATG	CsA, MTX	ATG, Tacrolimus, MMF
BM MC burden prior to alloHSCT, %	15-20 in BM smear, 30 in histology	20-25	~10
AlloHSCT outcome	d+35 post-alloHSCT, BM MC burden 32% Chimerism: 88% (d+35), 100% (d+1,019)	d+28 post-alloHSCT, BM MC burden 22% Chimerism: 95% (d+28), 100% (d+546)	d+189 post-alloHSCT, BM MC burden <5% Chimerism: 100% (d+734) *DNMT3A*, *SRSF2*, *TET2* negative, *KIT* D816V 17% in BM
Acute GVHD, grade	II (GI tract)	Suspected GVHD, DD infectious colitis	I (skin, face)
Other complications	VOD gr 2, acute kidney failure gr 1, CMV reactivation gr 1	Acute kidney failure, heart failure gr 2, cardiorenal syndrome with acute kidney failure gr 4, ischemic stroke gr 1, ascending colon colitis gr 2	Paroxysmal atrial fibrillation, CMV reactivation, rhinovirus infection, Covid-19 infection

ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CsA, cyclosporine A; d, day; DD, differential diagnosis; GI, gastrointestinal; GVHD, graft versus host disease; gr, grade; MTX, methotrexate; MC, mast cell; MMF, mycophenolate mofetil; TBI, total body irradiation; VOD, veno-occlusive disease.

Table 4. Treatment history post-alloHSCT

Treatment	Patient 1	Patient 2	Patient 3	Summary
Midostaurin	• **Started** 4 months post-alloHSCT, 50 mg 1-0-1 • **Duration of treatment** was 8 months; discontinued 1 month before starting avapritinib • **Discontinued** due to PD and disease relapse • **Response** was PD	• Did not receive midostaurin post-alloHSCT	• **Started** 3 months post-alloHSCT, 25 mg 3-0-3 • **Duration of treatment** was 8 months; discontinued 1 month prior to starting avapritinib • **Discontinued** due to toxicity (neutropenia) • Response was PD	• 2 patients who received midostaurin post-alloHSCT discontinued due to PD or toxicity
Avapritinib	• **Started** 1 year post-alloHSCT, 200 mg daily; dose reduced to 50 mg daily due to grade 3 thrombocytopenia • **Duration of treatment** was 26 months • **Discontinued** due to relapse of angiosarcoma (unrelated to treatment) leading to death	• **Started** 3 months post-alloHSCT, 200 mg daily with no dose modifications • **Duration of treatment** was 17 months • **Discontinued** due to grade 4 COVID-19 pneumonia and *E. coli* sepsis (unrelated to treatment) leading to death	• **Started** 1 year post-alloHSCT, 100 mg daily • Treatment is **ongoing** (>1 year, 10 months) with no dose modifications	• All patients received avapritinib post-alloHSCT

PD, progression of disease; PR, partial response.

Figure 2. Response to avapritinib post-alloHSCT: total mast cells in BM, *KIT* D816V VAF (A, D, G), alkaline phosphatase, basal serum tryptase (B, E, H), and hemoglobin, platelets (C, F, I)

Table 5. Responses to avapritinib post-alloHSCT

Treatment	Patient 1	Patient 2	Patient 3	Summary
Avapritinib	• Sustained decrease in bone marrow mast cell % and basal serum tryptase level • Alkaline phosphatase level stabilized • Best response at discontinuation was CRh per mIWG criteria[2]	• Sustained decrease in bone marrow mast cell %, *KIT* D816V VAF, and basal serum tryptase level (from 146 µg/L at screening to 20.9 µg/L at discontinuation) • This patient was not evaluable by mIWG criteria[2]	• Sustained decrease in bone marrow mast cell %, *KIT* D816 VAF, basal serum tryptase and alkaline phosphate levels • Best response of CR per mIWG criteria[2]	• All patients experienced deep and durable responses as measured by markers of mast cell disease burden

CR complete response; CRh, complete remission with partial hematologic recovery; VAF, variant allele frequency.

Table 6. Safety of avapritinib post-alloHSCT

Treatment	Patient 1	Patient 2	Patient 3	Summary
Avapritinib	• Most AEs were grade 1/2 • Grade ≥3 treatment-emergent AEs included anemia, angiodysplasia, and melanoma (all not related) and thrombocytopenia and increased gamma-glutamyl transferase (both related to treatment) • Required dose reduction due to grade 2/3 thrombocytopenia • Platelets rose post-alloHSCT to 158 × 10^9/L at discontinuation • 3 platelet transfusions were received due to SM-related thrombocytopenia	• Most AEs were grade 1 • Grade ≥3 treatment-emergent AEs included acute kidney injury, COVID-19 pneumonia, and *E. coli* sepsis (all not related); no grade ≥3 treatment-related AEs • No dose modifications • Platelets were 171 × 10^9/L at discontinuation • 2 platelet transfusions were received shortly after alloHSCT (prior to starting avapritinib) due to SM-related thrombocytopenia	• Most AEs were grade 1/2 • No grade ≥3 treatment-related AEs • No dose modifications • This patient received several platelet transfusions for disease-related thrombocytopenia prior to alloHSCT • 2 platelet transfusions were received shortly after alloHSCT • Thrombocytopenia resolved after alloHSCT and neutrophil counts stabilized at >1,000/µL	• The safety profile of avapritinib post-alloHSCT was favorable • Most AEs related to avapritinib were grade 1/2 and only one patient required dose modification • The most frequent grade ≥3 treatment-related AE, observed in one patient, was thrombocytopenia and was managed with dose modification • No treatment-related AEs led to treatment discontinuation

AEs, adverse events; SM, systemic mastocytosis.

References

1. Evans EK et al. *Sci Transl Med*. 2017;9(414):eaao1690.
2. Gotlib J et al. *Blood*. 2013;121:2392–2401.
3. DeAngelo D et al. *Nat Med*. 2021;27:2183–2191.
4. Gotlib J et al. *Nat Med*. 2021;27:2192–2199.
5. Blueprint Medicines Corporation. AYVAKIT Prescribing Information. 2023.
6. Ustun C et al. *J Clin Oncol*. 2014;32:3264–3274.
7. Ustun C et al. *Biol Blood Marrow Transplant*. 2016;22:1348–1356.
8. Lübke J et al. *Leukemia*. 2024; doi.org/10.1038/s41375-024-02186-x
9. Sriskandarajah P et al. *Curr Res Transl Med*. 2023;71(3):103398.
10. Sorror ML et al. *Blood*. 2005;106:2912–2919.

Acknowledgements

We thank the patients and their families for making this trial possible. We thank the investigators and clinical trial teams who participated in the trial. This study was supported by Blueprint Medicines Corporation, Cambridge, MA. Medical writing and editorial support was provided by William Sinkins, PhD, of ProEd Communications, supported by Blueprint Medicines Corporation, Cambridge, MA, according to Good Publication Practice guidelines.

Disclosures

Study sponsored by Blueprint Medicines. Deborah Christen received honoraria from Blueprint Medicines and AstraZeneca; consultancy funding from BeiGene, Blueprint Medicines, Pfizer, and Novartis; travel support from Amgen and Janssen. Johannes Lübke has nothing to disclose. Juliana Schwaab received honoraria from Blueprint Medicines and Novartis; consultancy funding from Blueprint Medicines. Anne Kaiser received consultancy and honoraria from Blueprint Medicines. Svetlava Rylova, Saša Dimitrijević, and Ilda Bidollari are employees of Blueprint Medicines Corporation. Jens Peter Panse received funding for consultancy, speakership, and/or scientific advisory boards from Alexion, Apellis, AstraZeneca, Blueprint Medicines Corporation, Boehringer Ingelheim, Bristol Myers Squibb, Chugai Pharmaceutical, F. Hoffmann-LaRoche, Novartis, Pfizer, and Sanofi-Pasteur. Andreas Reiter received consultancy funding from Blueprint Medicines Corporation, Cogent Therapeutics LLC, and Novartis Pharma; grants (institution) from Blueprint Medicines Corporation and Novartis Pharma.

Conclusions

- In this retrospective chart review, avapritinib use is feasible in patients with AdvSM post-alloHSCT, with durable responses and reduction of objective disease burden markers
- The safety profile of avapritinib was consistent with previously published reports, and no new safety concerns emerged in these patients. However, patients should be closely monitored as clinically indicated for thrombocytopenia and/or transplant-related complications
- Further studies are needed to evaluate optimal use of avapritinib post-alloHSCT

Presented at the **50th Annual Meeting of the EBMT**, April 14-17, 2024, Glasgow, Scotland, UK.