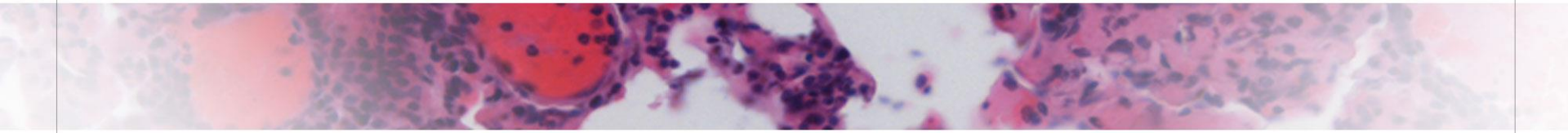
American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



# Effective Control of Advanced Systemic Mastocytosis with Avapritinib: Mutational Analysis from the EXPLORER Clinical Study

**Michael W. Deininger**, MD, PhD,[1] Daniel J. DeAngelo, MD, PhD,[2] Deepti H. Radia, MD,[3] Tracy I. George, MD,[4] Guang Yang, PhD,[5] Jayita Sen, PhD,[5] Hui-Min Lin, PhD,[5] Brenton G. Mar, MD, PhD,[5] Jason Gotlib, MD, MS[6]

[1]*Versiti Blood Research Institute and Medical College of Wisconsin, Milwaukee, WI, USA*;
[2]*Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*; [3]*Guy's & St Thomas' NHS Foundation Trust, London, UK*;
[4]*ARUP Laboratories, University of Utah, Salt Lake City, UT, USA;* [5]*Blueprint Medicines Corporation, Cambridge, MA, USA;*
[6]*Stanford Cancer Institute/Stanford University School of Medicine, Stanford, CA, USA*

# Disclosures

**Honorarium or consultancy fees:** Blueprint Medicines Corporation, Incyte, Medscape, Sangamo, Takeda, DisperSol, Fusion Pharma, Novartis

**Research funding:** Blueprint Medicines Corporation, Incyte, Leukemia & Lymphoma Society, Novartis, Pfizer, SPARC, Takeda

**Study management committees:** Blueprint Medicines Corporation and Takeda

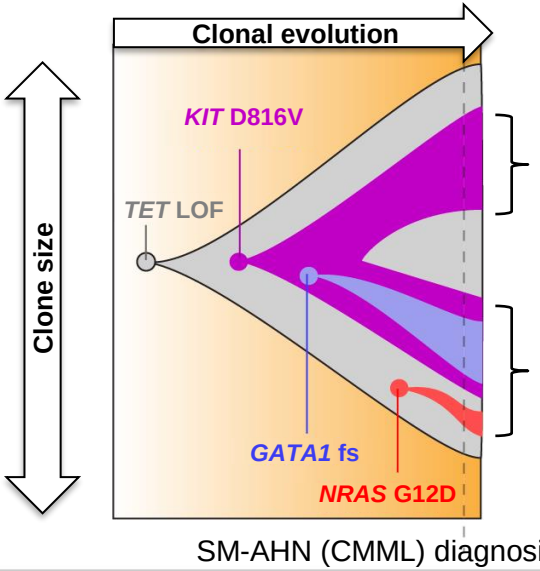
Study sponsored by Blueprint Medicines Corporation

AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including *PDGFRA* D842V mutations, and for the treatment of adults with advanced systemic mastocytosis (limitation of use: patients with platelets count ≥$50 \times 10^9$/L).

In Europe, AYVAKYT® (avapritinib) is approved by the European Medicines Agency (EMA) for the treatment of adult patients with unresectable or metastatic GIST harboring the *PDGFRA* D842V mutation.

# Advanced systemic mastocytosis (AdvSM) is a rare hematologic neoplasm driven by *KIT* D816V in ~95% of cases

- Patients have complex genomics with multiple clones and co-mutations[1,a]
- ~60–70% of patients have a distinct, associated hematological neoplasm (SM-AHN)[2]
- Patients with SM-AHN have poor outcomes, with only a 49% two-year survival rate following treatment with midostaurin[3]
- Disease progression and mortality may occur due to the SM, AHN, or both[4]




Neoplastic mast cell clones are driven by *KIT* D816V

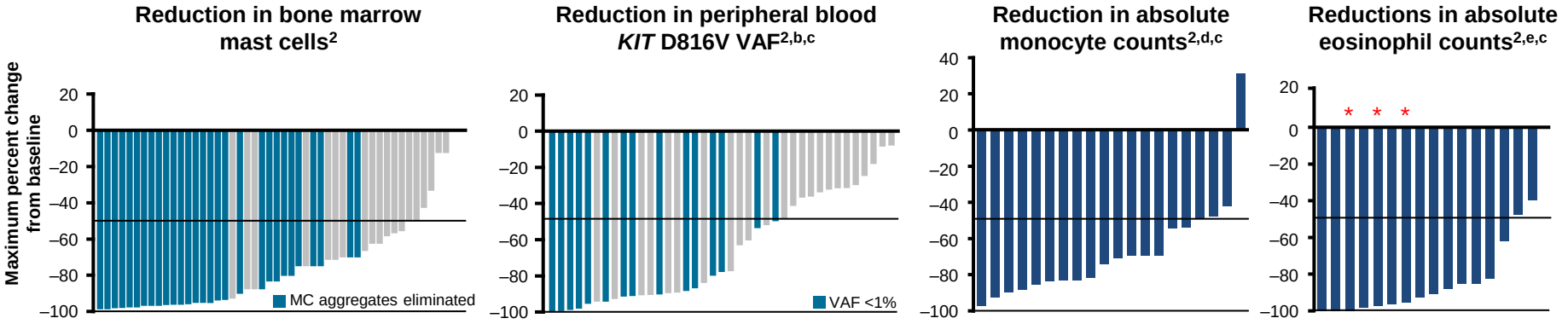
AHN clones (i.e., neoplastic monocytes in CMML) often have *KIT* D816V ± additional co-mutations



[a]Of note, non-advanced SM patients typically have only the *KIT* D816V mutation.
AHN, associated hematological neoplasm; CMML, chronic myelomonocytic leukemia; SM, systemic mastocytosis.
1. Jawar M et al. *Leukemia* 2015;29:1115–1122; 2. Shomali W & Gotlib J. *Int J Mol Sci* 2021;22:2983; 3. Gotlib J et al. *N Engl J Med*. 2016;374:2530–2541 (supplement); 4. Gotlib J et al. *Nat Med*. 2021 (in press).

# Avapritinib, a selective KIT D816V inhibitor, induced deep SM responses, including activity in patients with SM-AHN

- 75% response rate by mIWG-MRT-ECNM criteria[a], including 100% in ASM, 76% in SM-AHN and 69% in MCL[1]
- Responses regardless of prior therapy or high-risk *SRSF2*/*ASXL1*/*RUNX1* (*S*/*A*/*R*) co-mutations[1]
- Generally well tolerated[1]
- Activity observed in mast cell and non-mast cell lineages, including reductions in the *KIT* D816V VAF[1,2]
- Patients with SM-AHN had a 67% two-year survival on avapritinib with 38 months median duration of response[1]




*SM-AHN patients with CEL

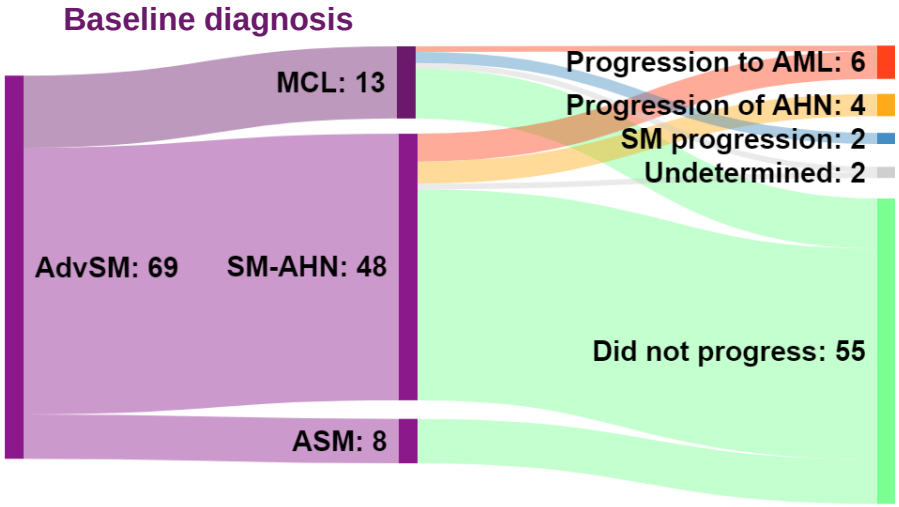


[a]CR, CRh, PR, or CI. [b]Patients with SM-AHN. [c]Ad hoc analysis. [d]Patients with SM-CMML. [e]Patients with baseline eosinophilia and SM-CEL.
ASM, aggressive systemic mastocytosis; CI, clinical improvement; CR, complete remission; CRh, complete remission with partial hematological recovery; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; MC, mast cell; MCL, mast cell leukemia; PR, partial remission; *S*/*A*/*R*, *SRSF2* / *ASXL1* / *RUNX1*; SM, systemic mastocytosis; SM-CEL, systemic mastocytosis with chronic eosinophilic leukemia; VAF, variant allele fraction.

1. DeAngelo D et al. *Nat Med*. 2021 (In press); 2. Reiter et al. EHA 2021.

# Exploratory analysis of reasons for progression

- EXPLORER (NCT02561988) is a phase I dose escalation study of avapritinib in 86 patients with local diagnosis of AdvSM, of which 69 were centrally confirmed[1]
- Avapritinib 30–400 mg was studied with expansion cohorts at 200 mg and 300 mg QD




- Only **14 (20%)** patients had clinical progression[a] on treatment
  - 10 (21%) patients with SM-AHN, 4 (31%) with MCL, and 0 with ASM had clinical progression
- Median duration of treatment was 9.5 months
- The majority were AHN or AML progressions in patients with baseline AHN
- Only 2 patients, both with MCL, had a SM progression



Data cut-off: May 27, 2020 (median follow-up of 23 months).
[a]As determined by investigator; a subset with AML met the mIWG-MRT-ECNM criteria definition for progressive disease.
AML, acute myeloid leukemia; mIWG-MRT-ECNM, (modified) International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; QD, once-daily.
1. DeAngelo D et al. *Nat Med*. 2021 [In press].

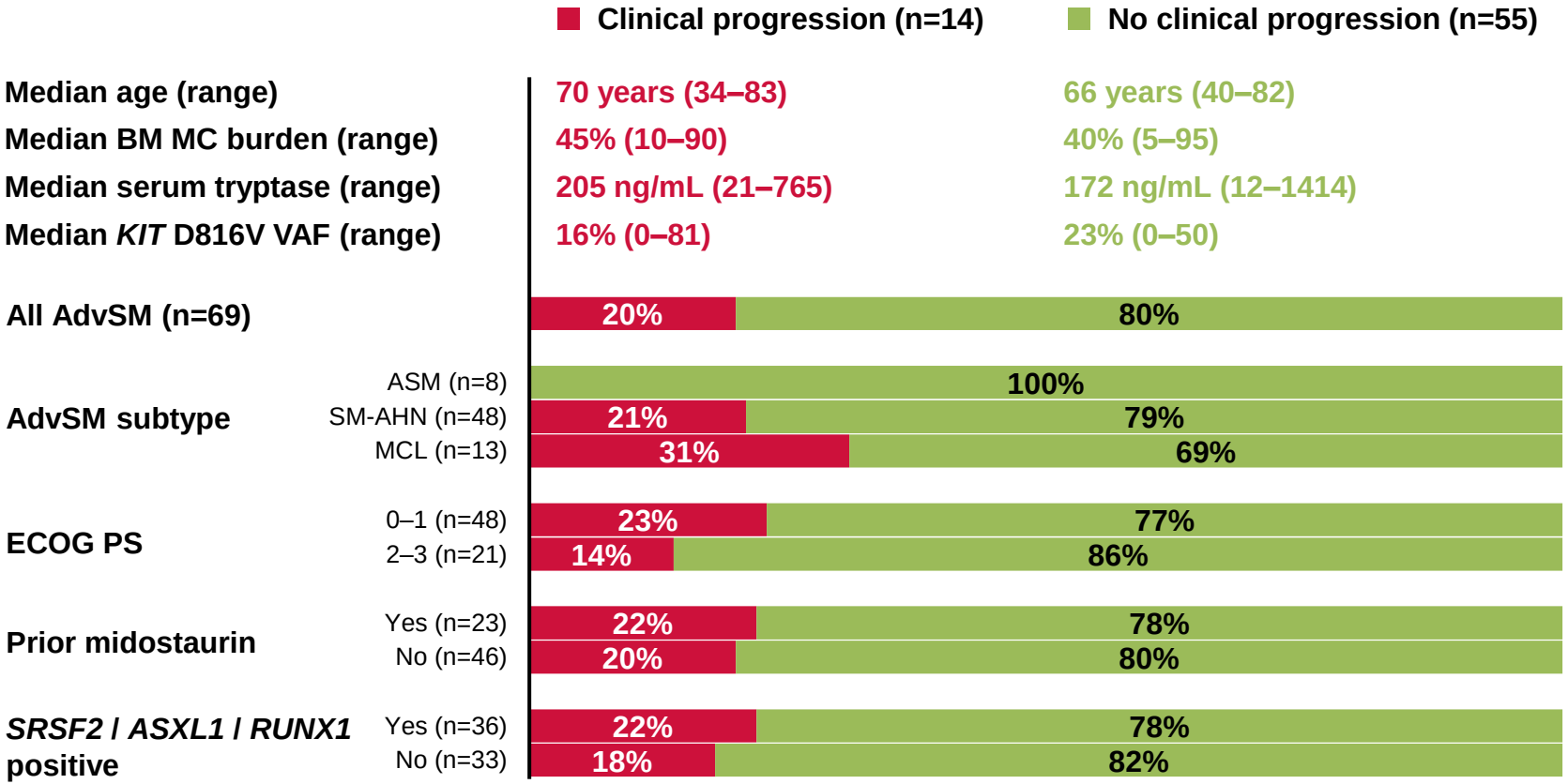
# Baseline characteristics

| Characteristic | All AdvSM (n=69) |
|---|---|
| **Median age, years (range) / Male, n (%)** | 67 (34–83) / 41 (59) |
| **ECOG PS 0–1 / 2–3, n (%)** | 48 (70) / 21 (30) |
| **Prior anti neoplastic therapy, n (%)** | 41 (59) |
| Midostaurin | 23 (33) |
| Cladribine | 10 (14) |
| ***KIT* D816V or Y positive, n (%)[a]** | 65 (94) |
| **Any myeloid co-mutation, n (%)** | 64 (93) |
| ***SRSF2* / *ASXL1* / *RUNX1* positive, n (%)** | 36 (52) |
| 1 / 2 / 3 genes mutated | 22 (32) / 11 (16) / 3 (4) |
| **Median BM MC burden, % (range)** | 40 (5–95) |
| **Median serum tryptase, ng/mL (range)** | 173 (12–1414) |
| **Median *KIT* D816V VAF, % (range)** | 17 (0–81) |

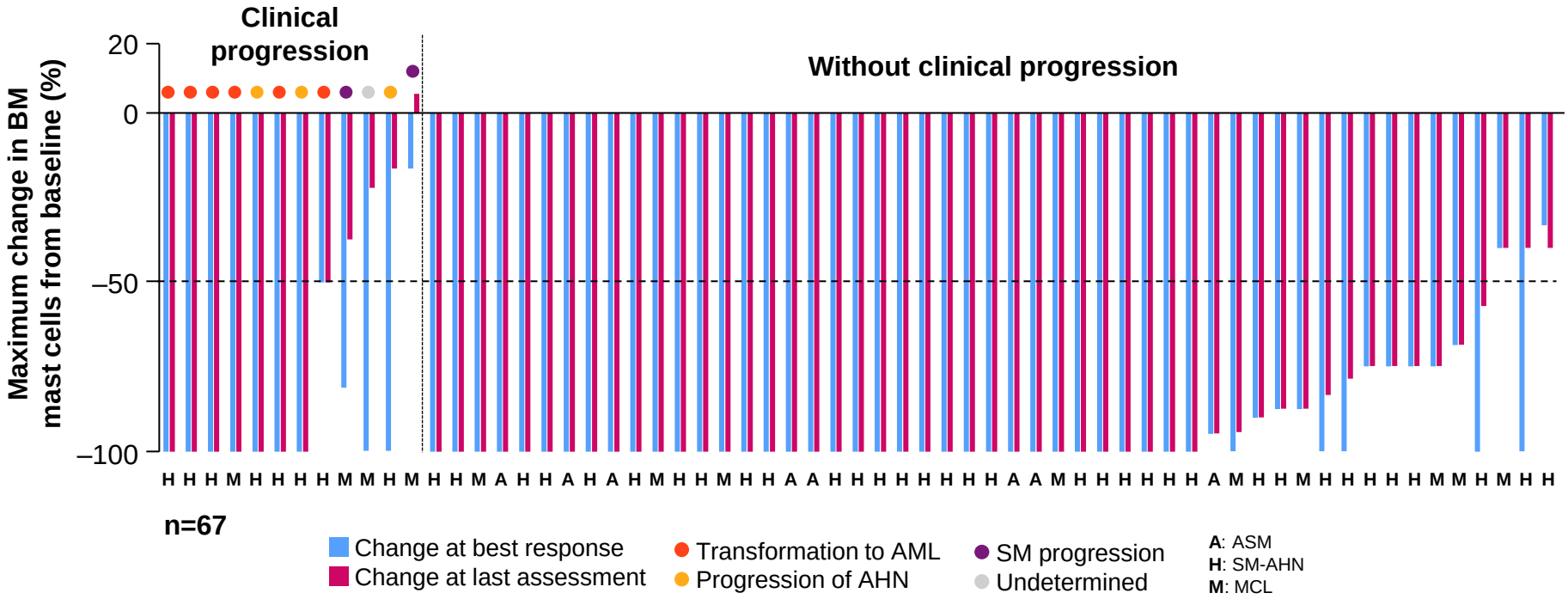


[a]Assessed by central D816V ddPCR assay and Trusight Myeloid Panel (for D816Y). VAF (%) assessed using validated ddPCR by central assay with limit of detection of 0.17%.
BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status.

# Baseline characteristics in patients with and without progression



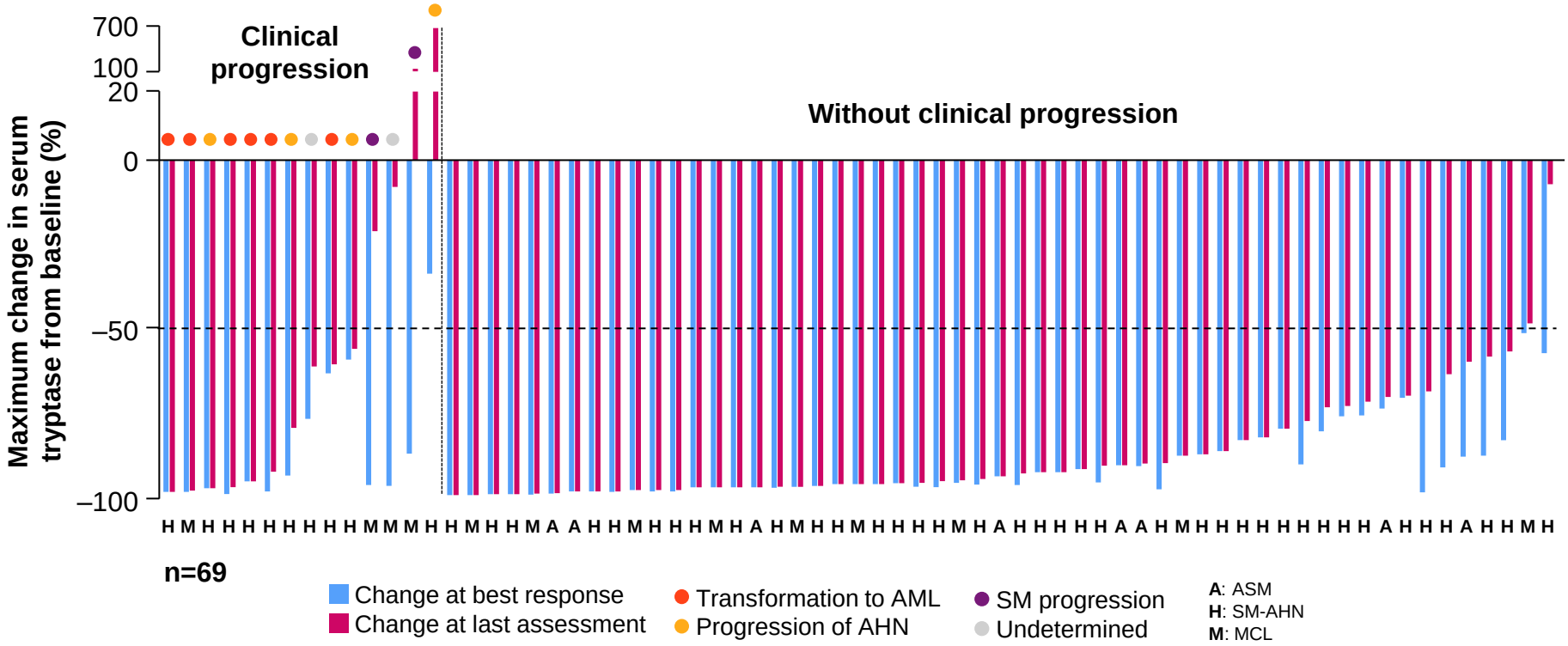
# Majority of patients had deep responses in bone marrow mast cell burden at last assessment regardless of progression






No statistical analysis conducted.

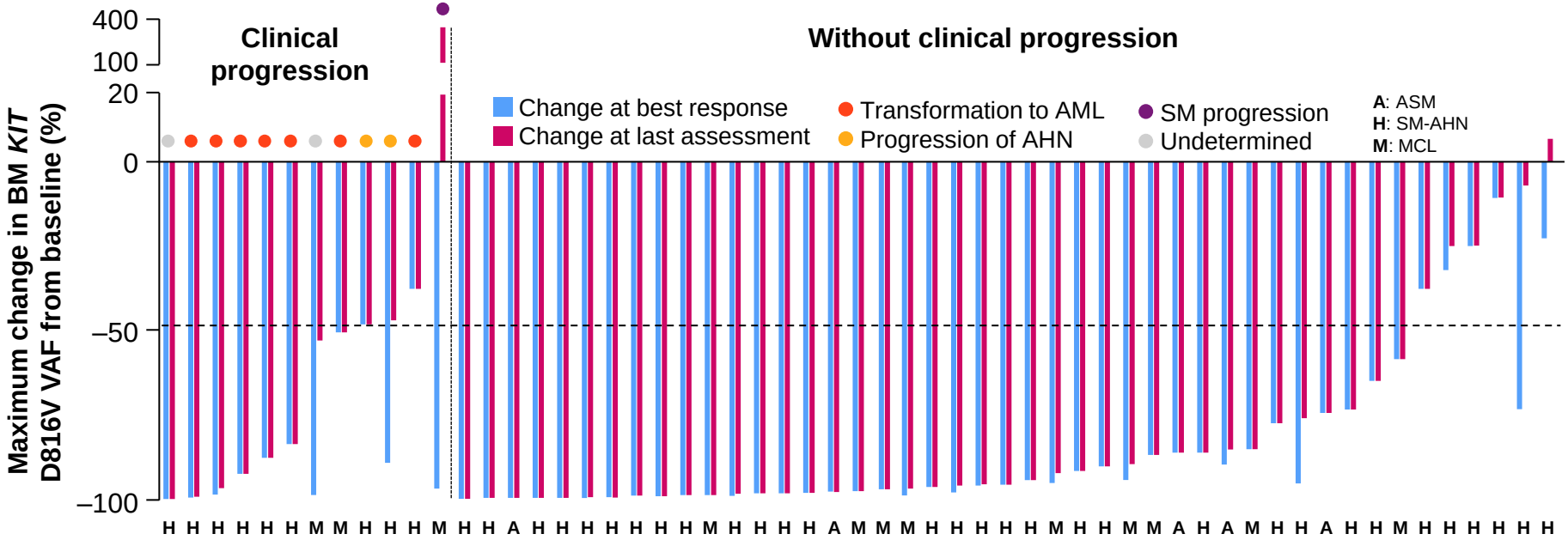
# Majority of patients had deep responses in serum tryptase at last assessment regardless of progression






No statistical analysis conducted.

# Majority of patients had deep responses in BM *KIT* D816V VAF at last assessment regardless of progression



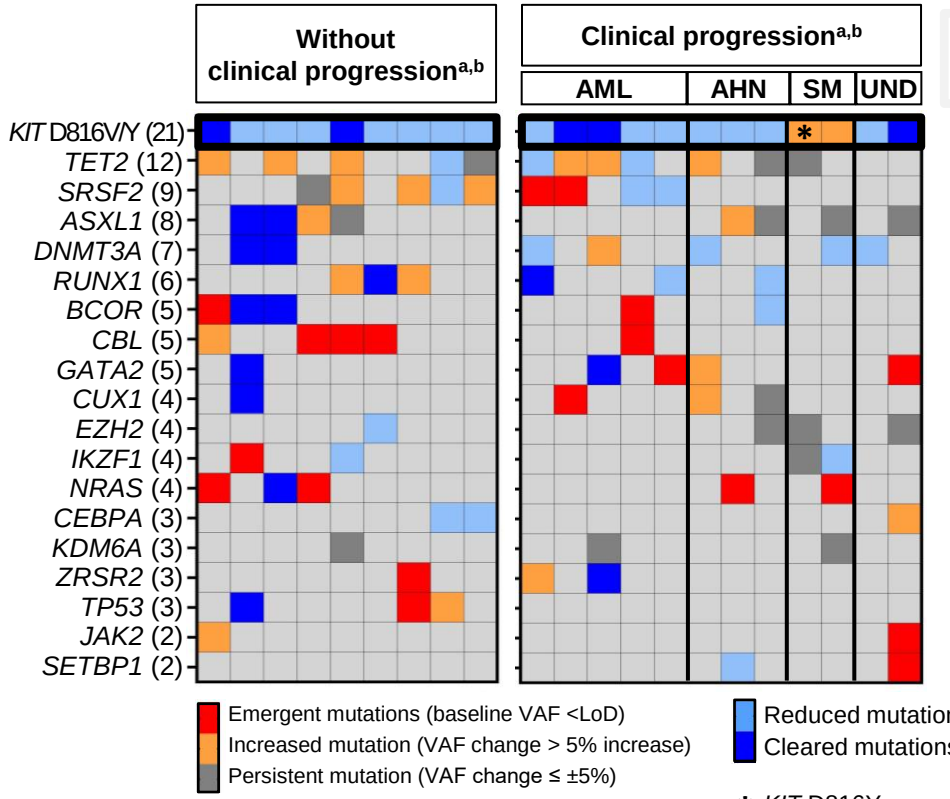

n=57

| | Clinical progression | Without clinical progression |
|---|---|---|
| BM *KIT* D816V VAF | 68% median reduction | 95% median reduction |
| >50% reduction | 67% of patients (8/12) | 87% of patients (39/45) |



No statistical analysis conducted.

# Complex pattern of co-mutation evolution regardless of outcome



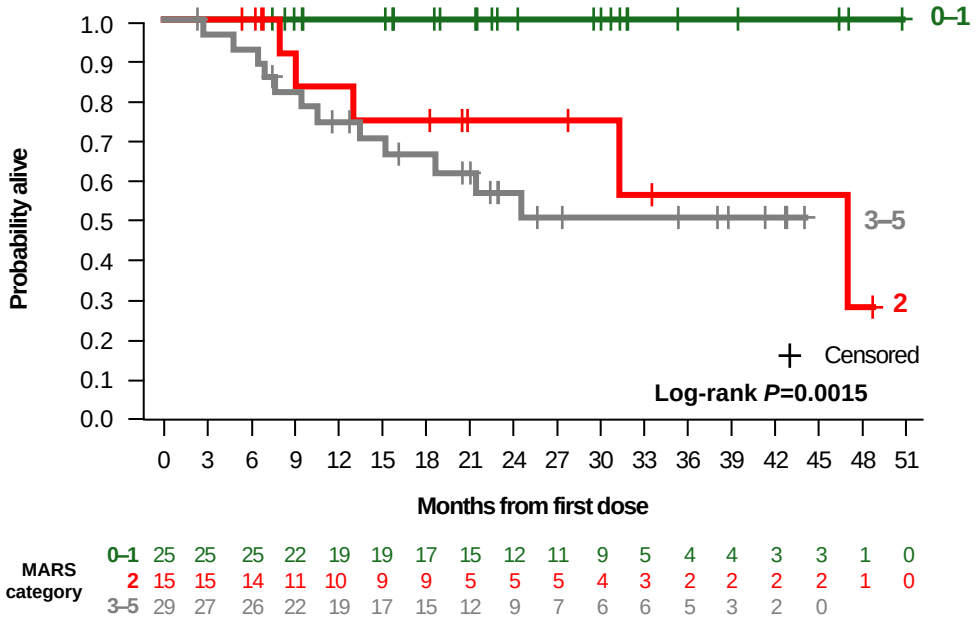

- TruSight™ Myeloid Panel at baseline in all patients and on study in a subset of patients with/without progression[a]

- 83% (10 of 12)[a] of progressions were not associated with increased *KIT* D816V/Y VAF
- 2 (17%) patients with baseline MCL had SM progressions with increased *KIT* D816V/Y VAF, but no additional mutations in *KIT* were identified
- No clear pattern of increasing or decreasing VAF was observed for most mutations



[a]Only a random subset of non-progressing patients had serial mutational profiling; 12 of 14 patients who progressed had serial profiling. [b]Other mutations found in single patients were *KRAS*, *SF3B1*, *U2AF1*, *ATRX*, *BCORL1*, *SMC3*, *NPM1*, *CDKN2A*, *STAG2*, *IDH1, IDH2, and MYD88.* LoD, limit of detection; UND, undetermined.

# Overall survival is more favorable in patients with a low baseline Mutation-Adjusted Risk Score (MARS)




MARS[1] is a validated, WHO-independent prognostic score based on 5 parameters:

1) >60 years of age
2) Anemia (Hgb <10 g/dL)
3) Thrombocytopenia (Plts <100× $10^9$/L)
4) 1 *S*/*A*/*R* mutation
5) ≥2 *S*/*A*/*R* mutations



Hgb, hemoglobin; Plts, platelets; WHO, World Health Organization.

1. Jawhar M et al. *J Clin Oncol*. 2019;37:2846–2856.

# Conclusions

- Avapritinib showed profound and durable reductions in objective disease burden in patients with AdvSM, in both the SM and AHN components
- With a median follow-up of 23 months, only 20% of patients have progressed on treatment, driven in most cases by *KIT* D816V-negative AHN clones
- Overall survival was more favorable in patients with lower baseline MARS scores
- In most patients who progressed, *KIT* D816V remained suppressed, suggesting a rationale for the addition of AHN-directed therapies
- These data highlight the potential value of single cell sequencing of SM and AHN components of AdvSM

# Acknowledgments


- Participating patients and families
- Avapritinib investigators and research coordinators
- Colleagues at Blueprint Medicines Corporation

- Medical writing support was provided by Kenny Tran, MSc, and editorial support was provided by Travis Taylor, BA, all of Paragon, Knutsford, UK, supported by Blueprint Medicines Corporation, Cambridge, MA, USA, according to Good Publication Practice guidelines