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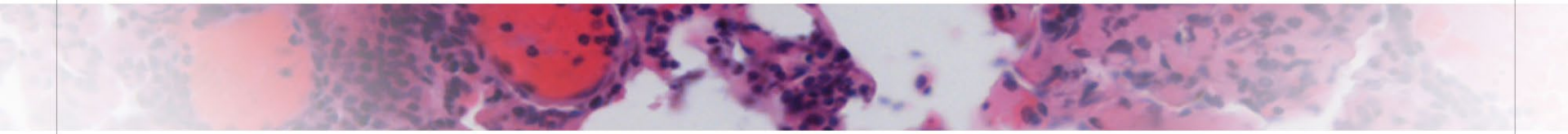

Pure Pathologic Response is associated with improved overall survival in patients with advanced systemic mastocytosis receiving avapritinib in the phase I EXPLORER study

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Disclosures

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Dr. Gotlib is the co-chair of the Study Steering Committee, received research funding, and served on advisory boards for Deciphera.

Study sponsored by Blueprint Medicines Corporation.

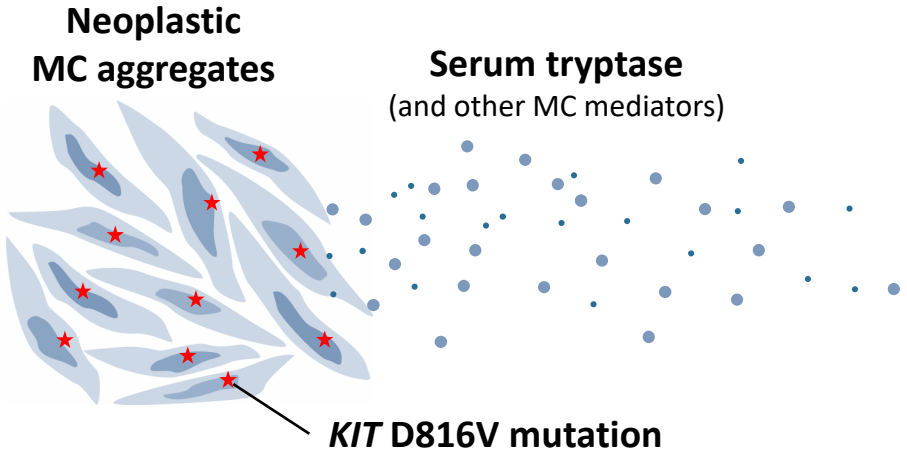
AYVAKIT™ (avapritinib) is approved by the US Food and Drug Administration (FDA) for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation, including *PDGFRA* D842V mutations.

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.

Avapritinib is not approved as safe or effective for use in systemic mastocytosis or any other indication by the FDA, EMA, or any healthcare authority in any jurisdiction.

AdvSM is a clonal hematologic neoplasm driven by *KIT* D816V

- AdvSM is characterized by elevated mast cell (MC) burden and organ damage (C-findings)[1]
- Complete remissions are rare (<1%) and the median overall survival is 29 months with the multikinase inhibitor midostaurin, the only approved therapy for AdvSM[2]
  - Estimated 1-, 2-, and 3-year overall survival rates were 72%, 53%, and 46%, respectively
  - Landmark analysis of response[a] after 6 cycles was not significantly associated with improved survival (*P*=0.18)



Organ damage (C-findings)

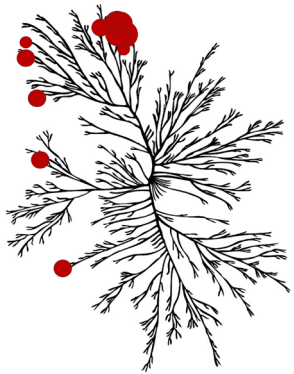
- Cytopenias
- Liver dysfunction
- Ascites, pleural effusions
- Splenomegaly with hypersplenism
- Malabsorption with weight loss
- Large osteolytic lesions/pathologic fractures

[a]Response as per Valent criteria (Valent P et al. *Eur J Clin Invest*. 2007;37:435–453).
AdvSM, advanced systemic mastocytosis; MC, mast cell.
1. Pardanani A. *Am J Hematol*. 2019;94:363–377; 2. Gotlib J et al. *N Engl J Med*. 2016;374:2530–2541.

Avapritinib, a potent and selective inhibitor of *KIT* D816V, induces deep reductions in MC burden and resolution of organ damage[1]

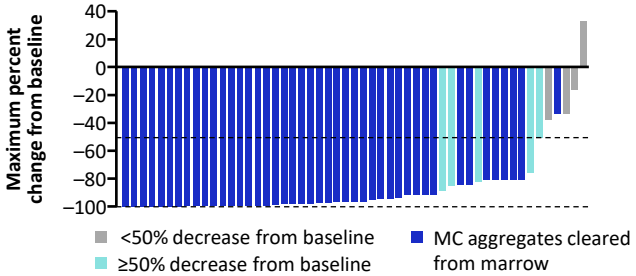
Highly potent against *KIT* D816V

Biochemical IC_{50}=0.27 nM[2]

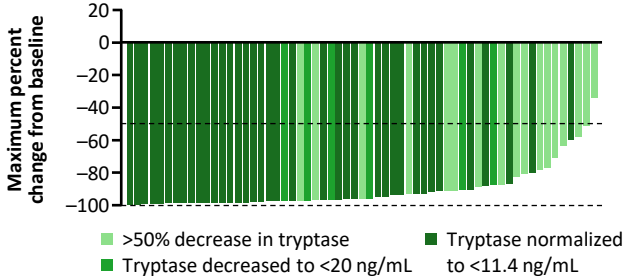


Highly selective kinome profile

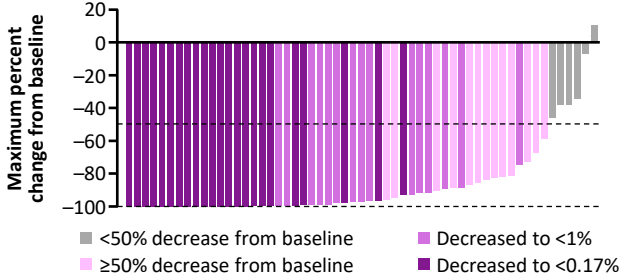
Bone marrow MCs



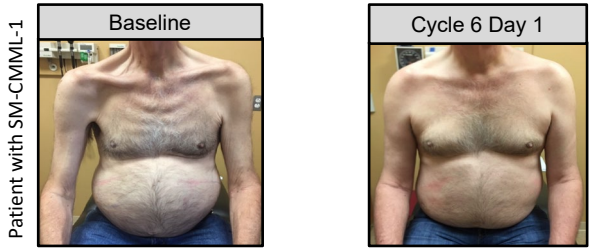
Serum tryptase



***KIT* D816V mutation allele fraction**



Resolution of organ damage (C-findings)



- Weight loss of >50 pounds
- Hypoalbuminemia (2.3 mg/dL)
- Ascites with paracentesis (15 L/week)

- All weight gained back
- Albumin normalized
- Ascites resolved

IC_{50}, half maximal inhibitory concentration; SM-CMML-1, chronic myelomonocytic leukemia type 1.

1. Gotlib J et al. Poster EP1079. Presented at the 25th European Hematology Association (EHA) annual congress, June 11–14 2020, Virtual; 2. Data on File.

Overall response rate by modified IWG-MRT-ECNM criteria

Best confirmed central response, n (%)	All evaluable (n=53)
ORR (CR + CRh + PR + CI)	**40 (75)**
CR or CRh[a]	**19 (36)**
Complete remission (CR)	8 (15)
CRh	11 (21)
Partial remission (PR)	18 (34)
Clinical improvement (CI)	3 (6)
Stable disease (SD)	12 (23)
Progressive disease (PD)	0
Not evaluable (NE)	1 (2)[b]

- BM MC aggregates eliminated
- Serum tryptase <20 ng/mL
- Resolution of palpable hepatosplenomegaly
- Full (CR) or partial (CRh) hematologic recovery
- **Full resolution of all evaluable C-findings**

- ≥50% reduction in BM MCs, serum tryptase
- **Full resolution of ≥1 evaluable C-findings**

- **Full resolution of ≥1 evaluable C-findings**

- Not in a CR, PR, CI or PD

- Worsening of evaluable C-findings or
- Progression to AML

All shown criteria for CR/CRh and PR need to be fulfilled[c]

All data in this presentation is as of a data cut-off of May 27, 2020

[a]Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* platelet count >50×10^9/L *and* Hgb level >8.0 g/dL. [b]Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks). [c]Response duration must be ≥12 weeks. ANC, absolute neutrophil count; AML, acute myeloid leukemia; BM, bone marrow; CRh, complete remission with partial hematologic recovery; Hgb, hemoglobin; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment; ORR, overall response rate.

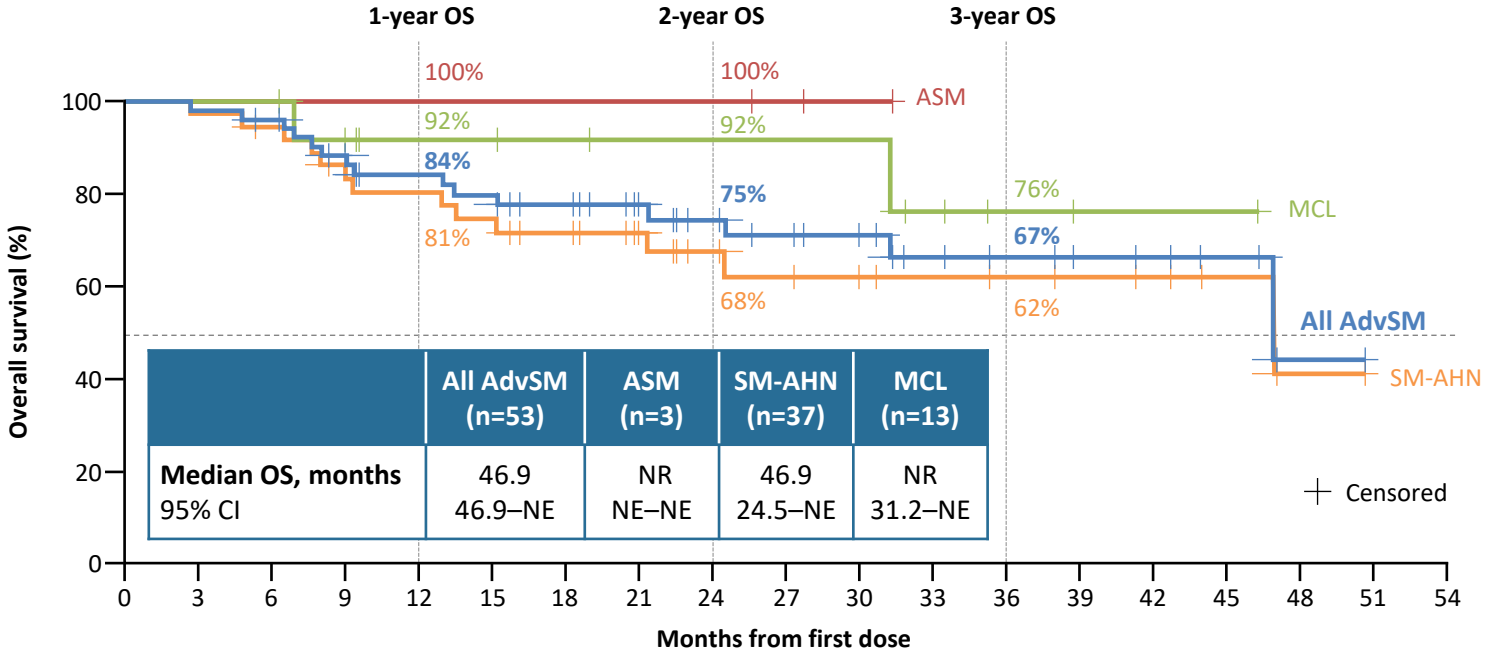
Overall response rate by modified IWG-MRT-ECNM criteria

Best confirmed central response, n (%)	All evaluable (n=53)	ASM (n=3)	SM-AHN (n=37)	MCL (n=13)	Midostaurin naïve (n=36)	Post midostaurin (n=17)
ORR (CR + CRh + PR + CI)	40 (75)	3 (100)	28 (76)	9 (69)	30 (83)	10 (59)
CR or CRh[a]	19 (36)	2 (67)	14 (38)	3 (23)	16 (44)	3 (18)
Complete remission (CR)	8 (15)	0	5 (14)	3 (23)	6 (17)	2 (12)
CRh	11 (21)	2 (67)	9 (24)	0	10 (28)	1 (6)
Partial remission (PR)	18 (34)	1 (33)	13 (35)	4 (31)	12 (33)	6 (35)
Clinical improvement (CI)	3 (6)	0	1 (3)	2 (15)	2 (6)	1 (6)
Stable disease (SD)	12 (23)	0	8 (22)	4 (31)	6 (17)	6 (35)
Progressive disease (PD)	0	0	0	0	0	0
Not evaluable (NE)	1 (2)[b]	0	1 (3)[b]	0	0	1 (6)[b]

All data in this presentation is as of a data cut-off of May 27, 2020

[a]Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* platelet count >50×10^9/L *and* Hgb level >8.0 g/dL.
[b]Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).
ASM, aggressive systemic mastocytosis; MCL, mast cell leukemia; SM-AHM, systemic mastocytosis with associated hematologic neoplasm.

Overall survival on avapritinib (efficacy population)



	All AdvSM (n=53)	ASM (n=3)	SM-AHN (n=37)	MCL (n=13)
Median OS, months	46.9	NR	46.9	NR
95% CI	46.9–NE	NE–NE	24.5–NE	31.2–NE

Patients at risk:

All AdvSM	53	52	50	43	39	37	33	26	22	19	16	12	9	7	6	4	1	0
ASM	3	3	3	3	3	3	3	3	3	2	1	0						
SM-AHN	37	36	34	30	28	26	23	17	13	11	9	8	7	6	5	3	1	0
MCL	13	13	13	10	8	8	7	6	6	6	6	4	2	1	1	1	0	

NR, not reached; NE, not estimable; OS, overall survival.

Primary basis of response in current AdvSM criteria is anchored to evaluable organ damage

IWG-MRT-ECNM criteria (2013)[1]

Measures full resolution in:

"Evaluable" C-findings

- Cytopenias (ANC, Hgb, platelets)
- Liver dysfunction (Dbil, AST/ALT, ALP)
- Hypoalbuminemia
- Ascites and pleural effusions
- Symptomatic splenomegaly (>5 cm)

Reductions in MC burden only sub-classifies response

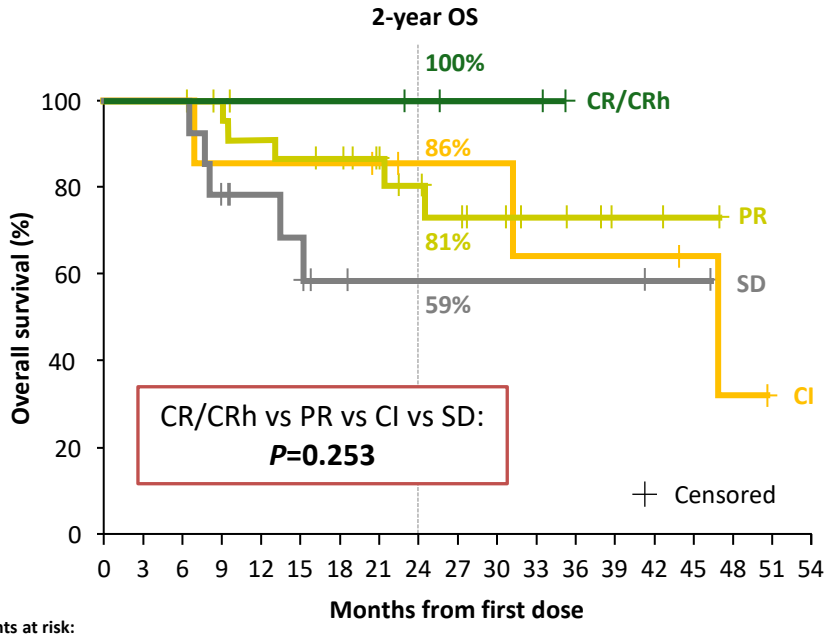
Challenges

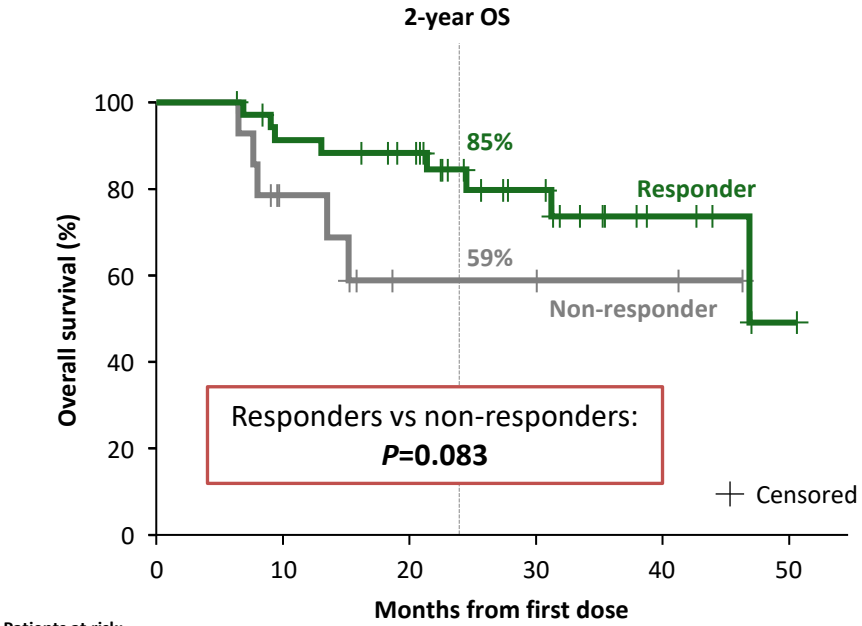
- Defining response by C-findings is complex and challenging due to their heterogenous nature[1,2]
- Geared more for clinical trials; more challenging in clinical practice
- Potential discordance between lingering non-hematologic C-findings but clearance of BM MCs
- Applicable to AdvSM patients who exhibit evaluable C-findings at baseline limiting the evaluable population
- Pathological or molecular responses may be more strongly associated with clinical outcomes such as survival[3] and favored by regulatory agencies[4]

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate transaminase; Dbil; direct bilirubin.

1. Gotlib J et al. *Blood*. 2013;121:2393–2401; 2. Pardanani A, Tefferi A. *Eur J Haematol*. 2010;84:371–378; 3. Jawhar M et al. *Blood*. 2017;130:137–145; 4. Kasamon YL et al. *Oncologist*. 2018;23:1511–1519.

mIWG-MRT-ECNM response trends toward association with improved survival: *Landmark analysis starting at end of Cycle 6*





Landmark analysis limited to mIWG-MRT-ECNM evaluable patients alive at end of Cycle 6 (n=50)

CI, clinical response; CR, complete remission; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasms Research and Treatment. PR, partial remission; SD, stable disease.

Proposed Pure Pathologic Response (PPR) criteria focuses on histopathological and molecular responses

PPR criteria

Measures resolution in:

Mast Cell Burden

- Neoplastic MC aggregates
- Serum tryptase
- *KIT* D816V mutation

Advantages

- Avoids challenges of complex C-finding assessments
- Can be easily used in routine clinical practice
- Can be used in any patient with measurable MC burden

Complete remission with full (CR) or partial (CRh) hematologic recovery[a]

- BM MC aggregates eliminated and tryptase <20 ng/ml

Molecular complete remission (mCR/mCRh)

- *and KIT* D816V mutant allele fraction falls below LOD by sensitive assay[b]

Partial remission (PR)

- ≥50% reduction in BM MCs and tryptase

Stable disease (SD)

- Not in a CR, PR, or PD

Progressive disease (PD)

- Transformation to AML

[a]Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* platelet count >50×10^9/L *and* Hgb level >8.0 g/dL..
[b]*KIT* D816V allele-specific polymerase chain reaction or digital droplet assay with sensitivity ~0.1%.
LOD, limit of detection; mCR, molecular complete remission; mCRh, molecular complete remission with partial hematologic recovery; PPR, pure pathologic response.

PPR criteria highlight depth of pathologic and molecular responses

Best confirmed central response, n (%)	All evaluable (n=53)	PPR criteria *in mIWG population* (n=53)	PPR molecular CRs
ORR (CR + CRh + PR + CI)	40 (75)	41 (77)	
CR or CRh[a]	19 (36)	25 (47)	13 (25)
Complete remission (CR)	8 (15)	12 (23)	6 (11)
CRh	11 (21)	13 (24)	7 (13)
Partial remission (PR)	18 (34)	16 (30)	
Clinical improvement (CI)	3 (6)	N/A	
Stable disease (SD)	12 (23)	12 (23)	
Progressive disease (PD)	0	0	
Not evaluable (NE)	1 (2)[b]	0	

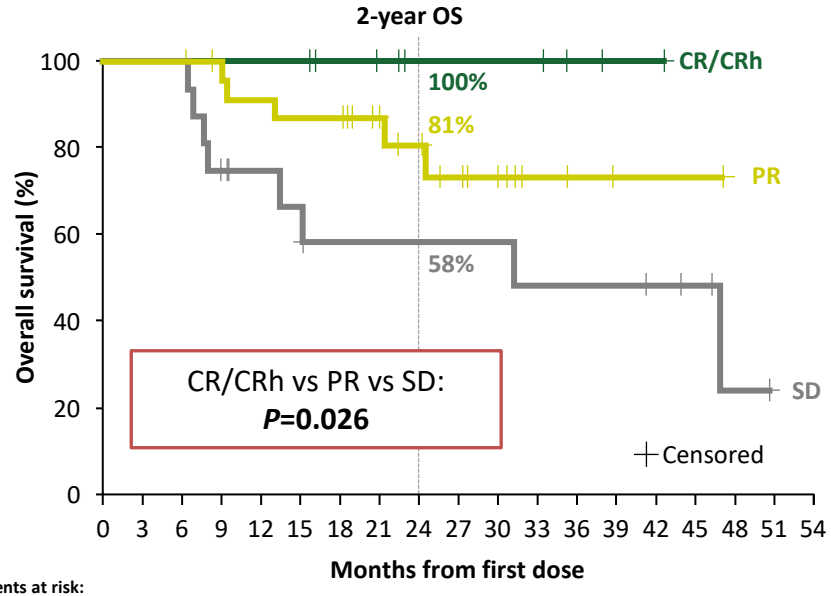
In addition, 11 additional AdvSM patients lacking evaluable mIWG C-findings are evaluable by PPR: **3 CR**, **3 CRh**, **3 PR**, and **2 SD**

- Similar ORR overall, but higher rate of CR/CRh rate by PPR compared with mIWG-MRT-ECNM criteria, demonstrating discordance between pathologic responses and assessment of clinical responses
- Molecular CR + CRh in 25% of patients by PPR criteria

[a]Partial hematologic recovery: ANC >0.5×10^9/L with normal differential (absence of neoplastic MCs and blasts <1%) *and* platelet count >50×10^9/L *and* Hgb level >8.0 g/dL.

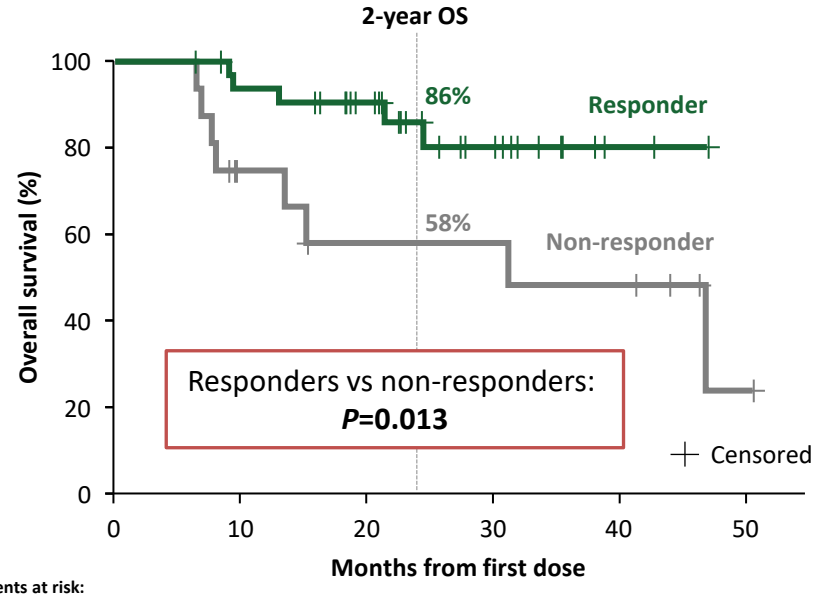
[b]Not evaluable due to ending study with insufficient follow-up for response assessment (<13 weeks).

PPR response is significantly associated with improved survival: *Landmark analysis starting at end of Cycle 6*



Patients at risk:

CR/CRh	9	9	9	9	9	9	7	6	4	4	4	4	2	1	1	0	
PR	25	25	25	23	21	20	20	14	12	9	6	3	2	1	1	1	0
SD	16	16	16	11	9	8	6	6	6	6	6	5	5	5	4	3	1	0



Patients at risk:

Responder	34	34	34	32	30	29	27	20	16	13	10	7	4	2	2	1	0
Non-responder	16	16	16	11	9	8	6	6	6	6	6	5	5	5	4	3	1	0

Landmark analysis limited to mIWG-MRT-ECNM evaluable patients alive at end of Cycle 6 (n=50) for comparison purposes of PPR to mIWG-MRT-ECNM criteria. In all PPR evaluable AdvSM patients alive at end of Cycle 6 (n=61), response is also **significantly associated with improved survival (*P*=0.005).**

Conclusions

- Proposed PPR criteria are simple, can be utilized in clinical practice, increases the number of evaluable patients, and are applicable to all AdvSM patients with measurable disease burden (e.g. BM mast cells and serum tryptase level)
- PPR response versus no response at end of Cycle 6 is correlated with overall survival (*P*=0.013)
- PPR should be explored as a primary endpoint for future trials
- Further analyses are required to compare overall survival using mIWG-MRT-ECNM versus PPR in specific subgroups (e.g. SM-AHN; midostaurin-naïve vs. prior midostaurin)

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- Participating patients and families
- Avapritinib investigators and research coordinators
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