Avapritinib, a Potent and Selective Inhibitor of KIT D816V, Induces Complete and Durable Responses in Patients with Advanced Systemic Mastocytosis

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EXPLORER Advanced SM

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Disclosures

Dr. Deepti Radia is an investigator for Blueprint Medicines' ongoing phase 1 and phase 2 studies in advanced, indolent and smoldering systemic mastocytosis

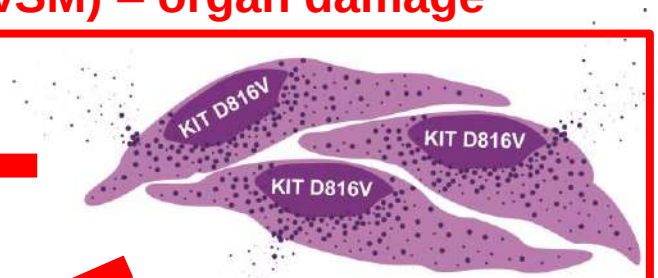
Dr. Radia has the following disclosures:
Consulting or advisory role: Blueprint Medicines, Novartis
Speaker's Bureau: Novartis

Avapritinib is an investigational agent discovered by and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

Systemic mastocytosis (SM) is a clonal mast cell disease

- *KIT* D816V drives mast cell growth and activation in ~95% of cases
- Mast cell activation leads to debilitating symptoms
- SM subtyping is based on clinicopathologic features and predicts survival[1-3]

Advanced SM (AdvSM) – organ damage



Mast cell leukemia
(MCL)
mOS: 2 months

SM with an associated hematological neoplasm
(SM-AHN)
mOS: 24 months

Aggressive SM
(ASM)
mOS: 41 months

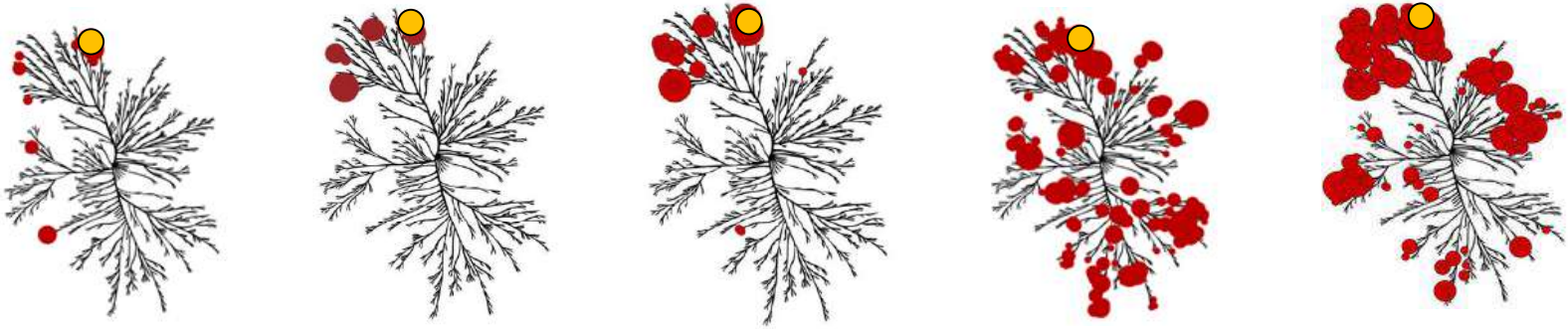
Indolent SM
(ISM)
*mOS: 198 months**

Smoldering SM
(SSM)
mOS: 120 months

1. Pardanani A. *Am J Hematol.* 2016;91(11):1146-1159. 2. Lim KH et al. *Blood.* 2009;113(23):5727-5736
3. Valent P et al. *Cancer Res*. 2017;77(6):1261-1270.

*Expected US survival for age
mOS: median Overall Survival

Avapritinib potently and selectively targets *KIT* D816V



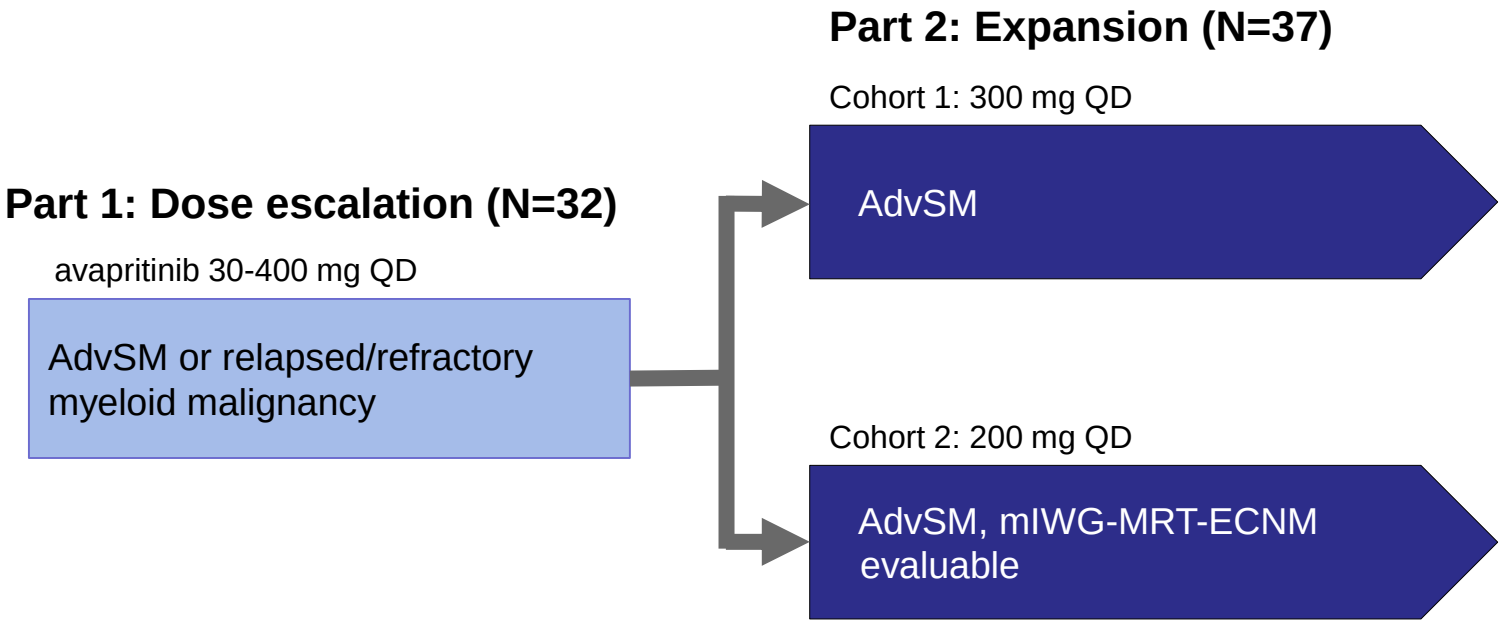
Binding to KIT Binding to other kinases (size is proportional to binding)

KIT D816V biochemical IC_{50}				
avapritinib*	imatinib*	masitinib#	midostaurin*	ripretinib#
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Biochemical binding by DiscoverRX at 3uM

*Evans EK et al. Sci Transl Med. 2017;9(414)
#Blueprint Medicines internal data on file

Phase 1 EXPLORER clinical trial design



Key entry criteria:

- AdvSM (ASM, SM-AHN or MCL) or relapsed/refractory myeloid malignancy per local assessment
- Age ≥18 years, ECOG performance status 0-3, platelets ≥25 x10^9/L

Study objectives:

- RP2D, safety, ORR per m-IWG-MRT-ECNM, patient-reported outcomes

EXPLORER Advanced SM

All data in this presentation are based on a cut-off of January 2, 2019; QD, once daily
RP2D, recommended Phase 2 dose, ECOG, Eastern Cooperative Oncology Group

Central pathology and adjudication implemented

EXPLORER trial now performing central adjudication for confirmation of diagnosis and consistency of response evaluation

Central Assessments

- ✔ Central tryptase and imaging
- ✔ Central adjudication of diagnosis and response
- ✔ Central pathology and mutation assessment
- ✔ Only responses confirmed ≥12 weeks considered

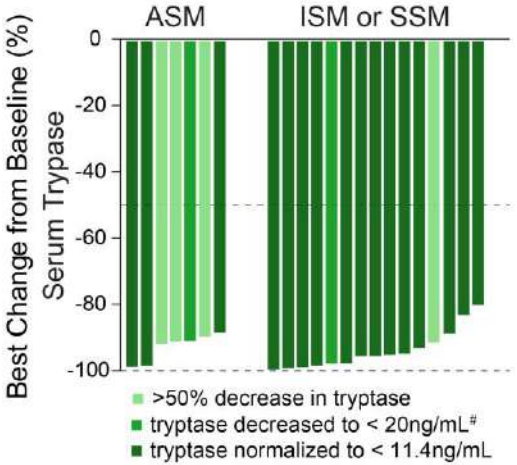
45% of local subtyping changed during central adjudication

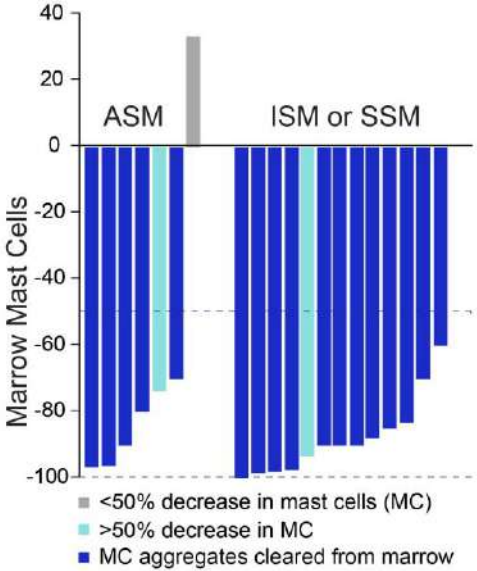
1. Found AHN on central pathology (i.e., ASM → SM-AHN, 20%)
2. WHO C-findings not present/documented upon review (ie. ASM → ISM, 19%)
3. Other central pathology discordance (i.e., MCL found, AHN not found, 6%)

WHO C-findings are complex and mis-subtyping common

- 13 of 34 local diagnoses of ASM were adjudicated to be ISM (12) or SSM (1) due to lack of WHO C-findings upon central review*
- Presence of WHO C-findings in ASM correlates with higher mast cell burden

Mast cell burden	ASM	ISM/SSM
n	7	15
Median tryptase, ng/mL	270	116
Median marrow biopsy mast cells, %	30	20





*Bone findings that were not large osteolytic lesions, weight loss that was <10% of body weight, splenomegaly, but without hypersplenism (ie. platelets <100K/uL) were most common

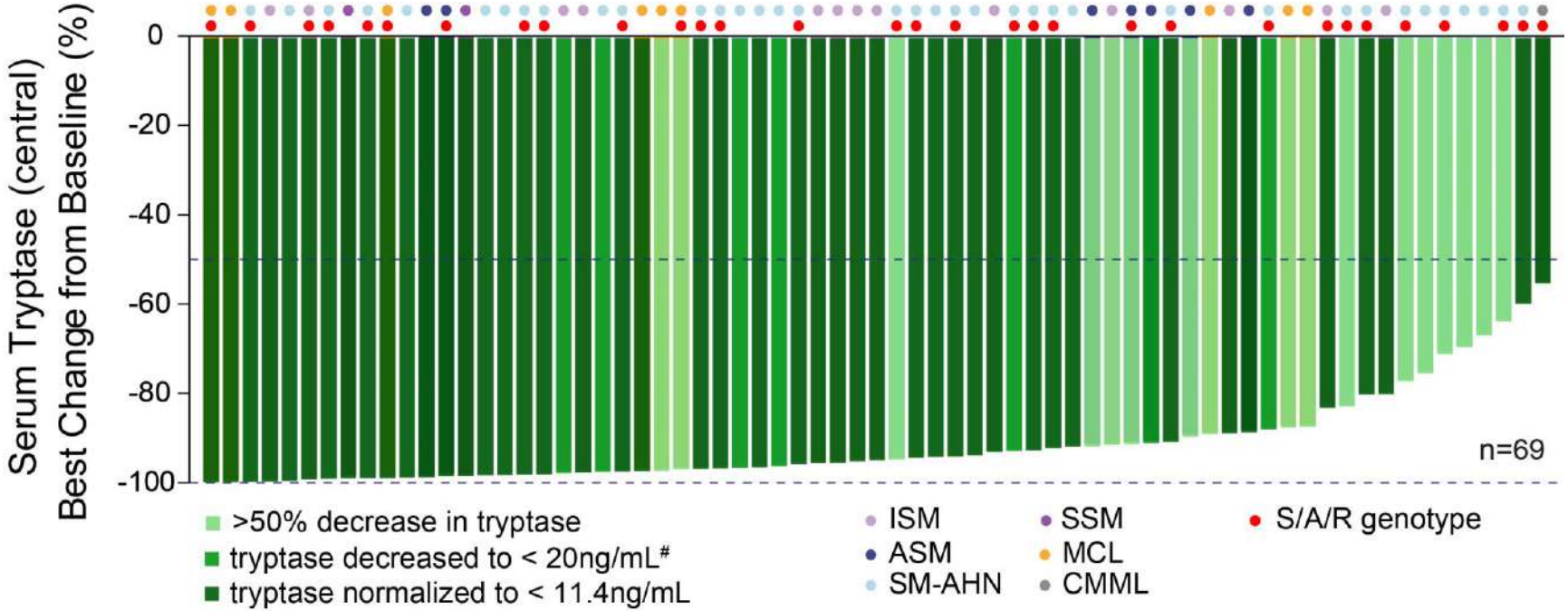
Baseline characteristics

Parameter		All patients (N=69)	mIWG Evaluable* pts (N=39)
Median age, years (range) / Female, n (%)		62 (34 – 83) / 33 (48)	66 (34 – 83) / 21 (54)
SM subtype per central assessment, n (%)*	AdvSM	53 (77)	39 (100)
	ASM	7 (10)	3 (8)
	SM-AHN	37 (54)	28 (72)
	MCL	9 (13)	8 (20)
	ISM or SSM	15 (22)	0
	Not SM (CMML)	1 (1)	0
ECOG performance status, n (%)	0-1	50 (75)	26 (67)
	2-3	17 (25)	13 (33)
KIT mutation, per central assays[#], n (%)	D816V positive	62 (90)	37 (95)
	D816Y positive	2 (3)	2 (5)
	KIT mutation negative	5 (7)	0
SRSF2, *ASXL1* and/or *RUNX1* (S/A/R) mutation positive, n (%), n=64		31 (45)	22 (56)
Prior anti-neoplastic therapy	Median # of therapies (range)	1 (0 – 4)	1 (0 – 4)
	Any, n (%)	42 (61)	23 (59)
	Midostaurin	15 (22)	10 (26)
	Cladribine	11 (16)	6 (15)
Bone marrow mast cell (MC) burden (%), median (range)		35 (5 – 95)	50 (5 – 95)
Serum tryptase (µg/L), median (range)		163 (12 – 1414)	182 (21 – 765)
KIT D816V allele fraction, median % (range)		9 (0 – 81)	16 (0 – 81)

*mIWG Evaluable patients have central diagnosis of AdvSM and adjudicated baseline mIWG-MRT-ECNM C-finding(s) (or MCL) and at least 25 weeks follow up (or EOS)

65% of patients return to normal tryptase levels

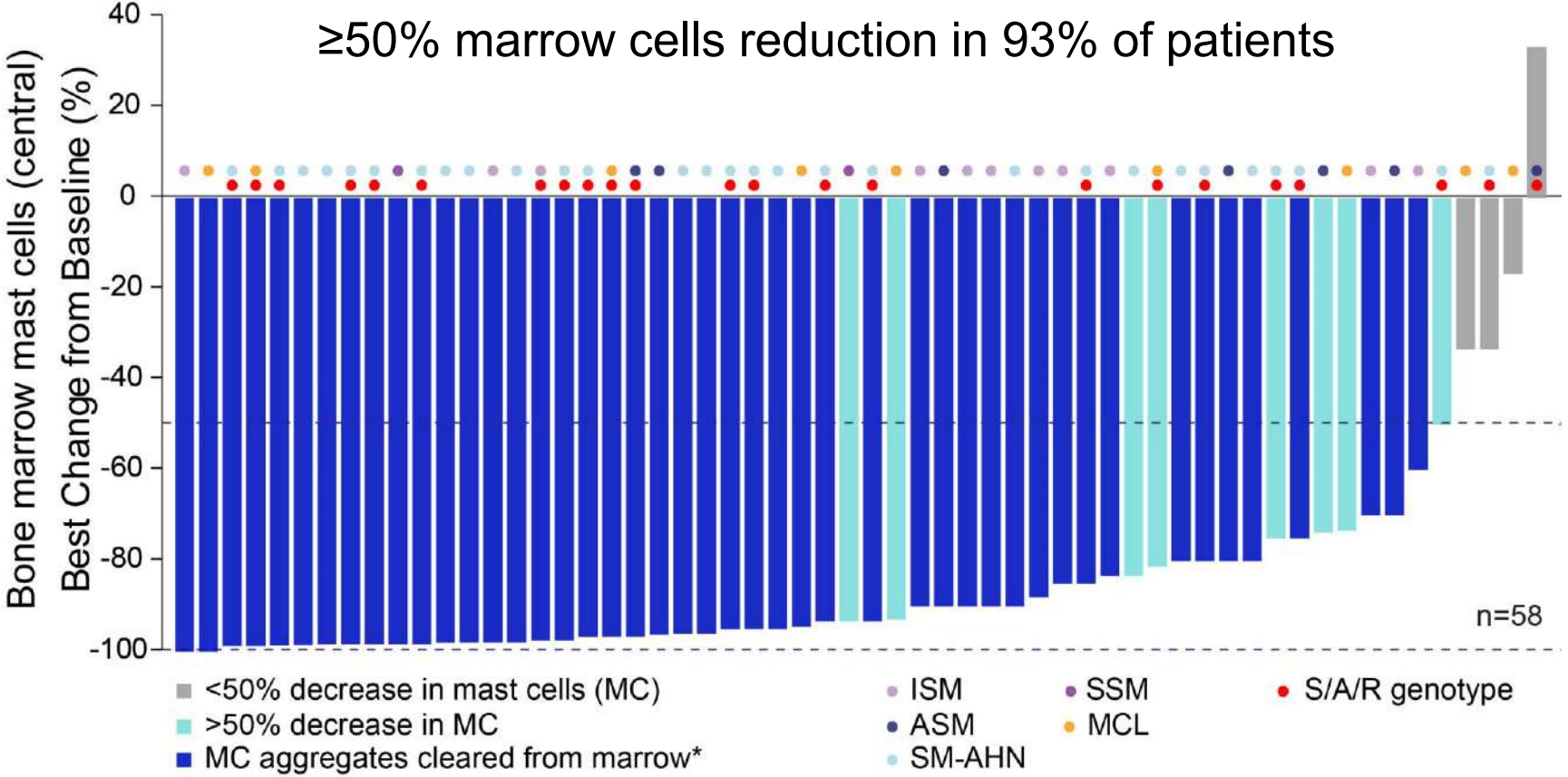
≥50% tryptase reduction in every patient treated



normal serum tryptase is defined as <11.4ng/mL

< 20ng/mL is a criterion for complete remission per mIWG-MRT-ECNM

79% of patients clear marrow mast cell aggregates

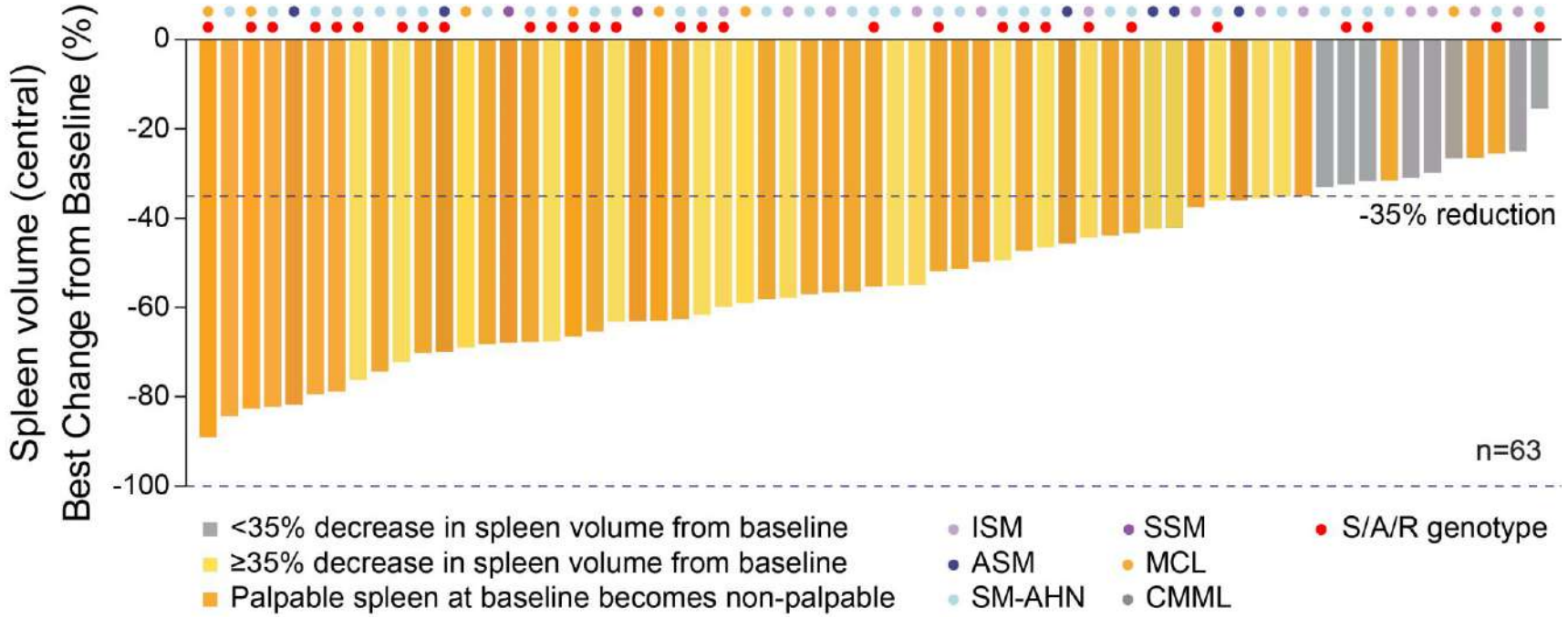


Only patients with MC aggregates at baseline who have post-baseline assessments included

* Clearance of marrow MC aggregates, but necessarily interstitial MC, is a criterion for complete remission per mIWG-MRT-ECNM

84% of palpable spleens become non-palpable

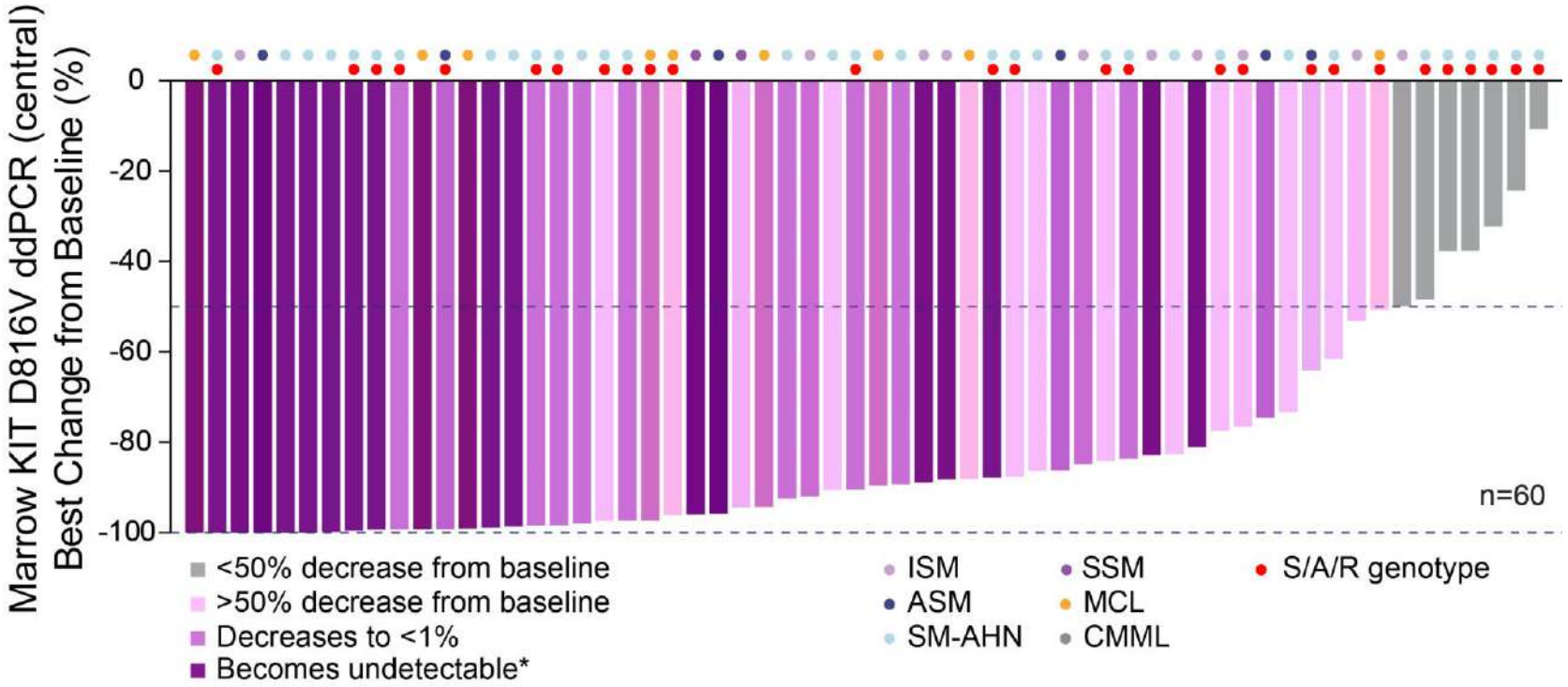
≥35% reduction in spleen volume in 81% of patients



Only patients with measurable spleens at baseline who have post-baseline assessments included
*Of 44 palpable spleens at baseline, 37 (84%) become non-palpable. One not shown on figure as no post-baseline scan yet

>50% reduction in marrow KIT D816V in 88% of patients

Marrow KIT D816V becomes undetectable in 33% of patients



Only patients with marrow KIT D816V at baseline who have post-baseline assessments included
*Allele fraction is below validated reliable threshold of detection for KIT D816V ddPCR assay of 0.17%

High rate of confirmed mIWG-MRT-ECNM responses across all AdvSM subtypes

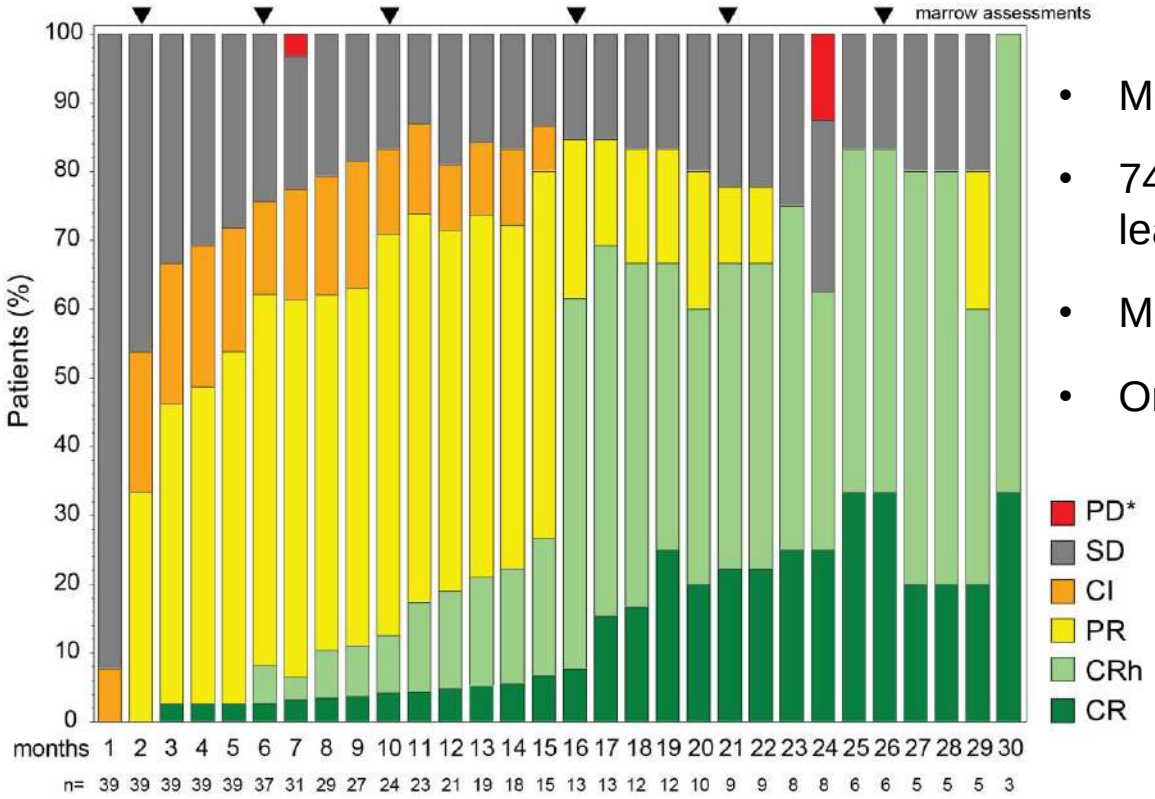
Best confirmed central response, n (%)	All evaluable (n=39)	ASM (n=3)	SM-AHN (n=28)	MCL (n=8)	S/A/R genotype (n=22)
mIWG ORR (CR + CRh + PR + CI)	**30 (77)**	**3 (100)**	**21 (75)**	**6 (75)**	**16 (73)**
CR or CRh[1]	9 (23)	0	7 (25)	2 (25)	5 (23)
Complete Remission (CR)	3 (8)	0	2 (7)	1 (13)	1 (5)
CR, partial hematologic recovery[1] (CRh)	6 (15)	0	5 (18)	1 (13)	4 (18)
Partial Remission (PR)	18 (46)	3 (100)	13 (46)	2 (25)	9 (41)
Clinical Improvement (CI)	3 (8)	0	1 (4)	2 (25)	2 (9)
Stable Disease (SD)	9 (23)	0	7 (25)	2 (25)	6 (27)
Progressive Disease* (PD)	0	0	0	0	0

All responses (CR, CRh, PR, CI) confirmed at ≥12 weeks

[1] CRh: Requires all criteria for CR be met and response duration must be ≥12 weeks (to be confirmed); however, patient may have residual cytopenias. The following are required for CRh: 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

S/A/R: A poor prognosis SRSF2, ASXL1 or RUNX1 mutation detected at baseline
*No patients were primary progressors within the first 12 weeks

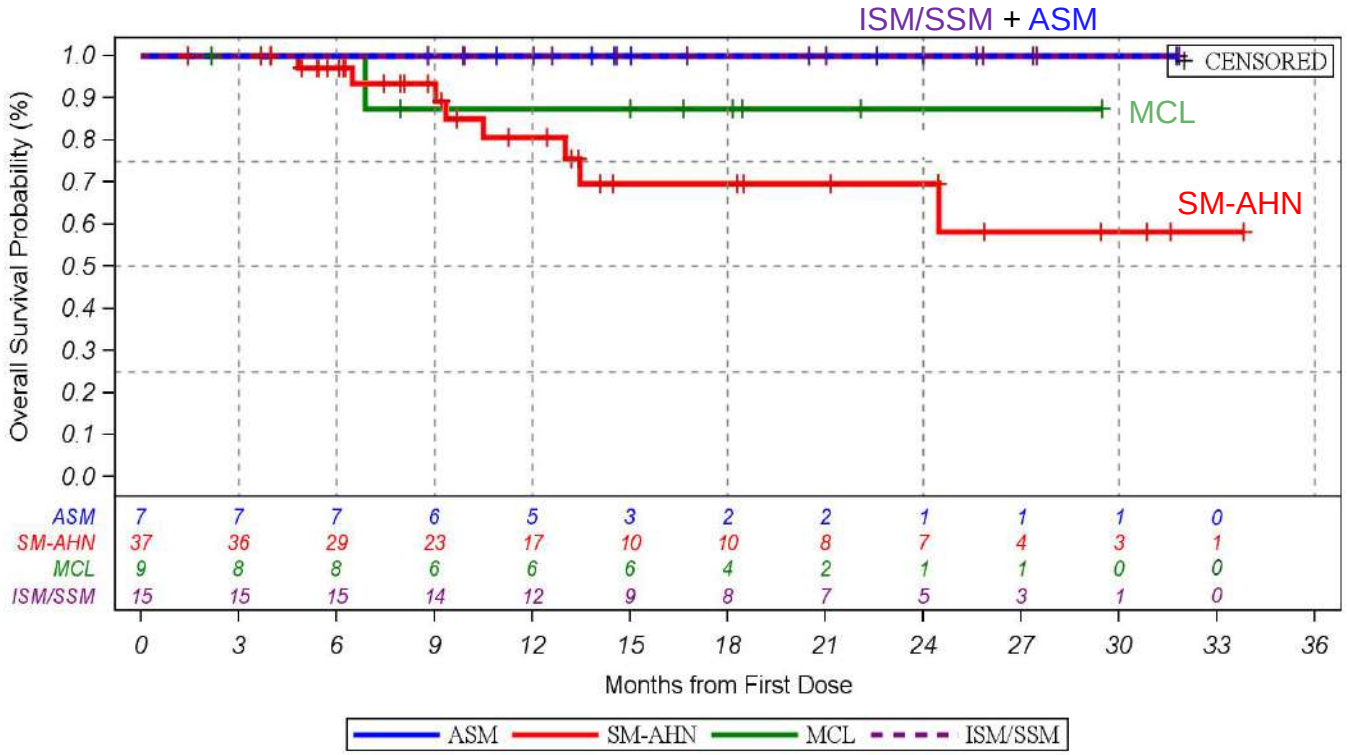
Responses occur rapidly and deepen over time



- Median time to initial response 2 months
- 74% of patients maintain response for at least 12 months
- Median time to CR/CRh is 16 months
- On therapy up to 34 months

*Only 3 pts met the mIWG-MRT-ECNM PD response criteria (all transformation to AML), however 6 additional clinical progressions also occurred

Median overall survival not reached for any subtype



Estimated
24 month OS rate

Subtype	%
All AdvSM	**78**
ASM	100
SM-AHN	70
MCL	88
ISM or SSM	**100**

Only patients with a central diagnosis of SM shown (n=68)

Treatment-emergent adverse events (AEs)

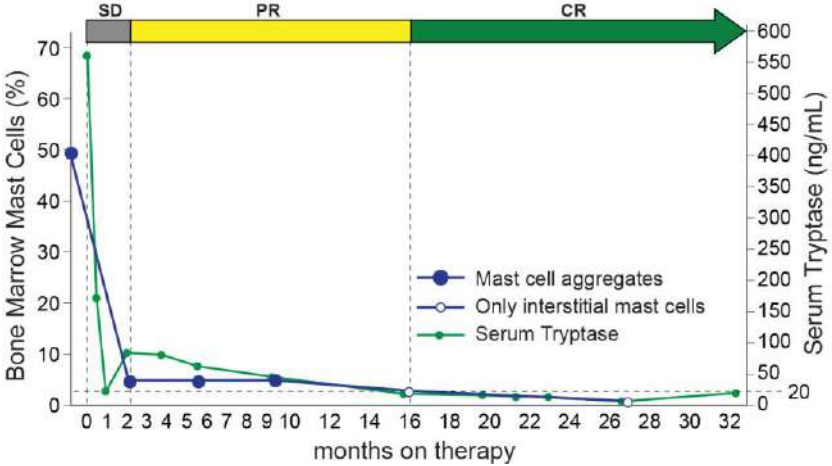
Adverse event, n (%)	Any Grade	Grade 3/4
NON-HEMATOLOGICAL AEs >15% (N=69)		
Periorbital edema	52 (75)	3 (4)
Diarrhea	28 (41)	1 (1)
Nausea	26 (38)	3 (4)
Fatigue	25 (36)	5 (7)
Peripheral Edema	23 (33)	0
Vomiting	22 (32)	3 (4)
Cognitive effects*	22 (32)	3 (4)
Hair color changes	20 (29)	1 (1)
Arthralgia	14 (20)	1 (1)
Abdominal pain	13 (19)	1 (1)
Dizziness	13 (19)	1 (1)
Decreased appetite	12 (17)	0
Pruritis	12 (17)	0
Constipation	11 (16)	1 (1)
Dysgeusia	11 (16)	0
HEMATOLOGICAL AEs >10% (N=69)		
Anemia	38 (55)	20 (29)
Thrombocytopenia	24 (35)	16 (23)
Neutropenia	8 (12)	7 (10)

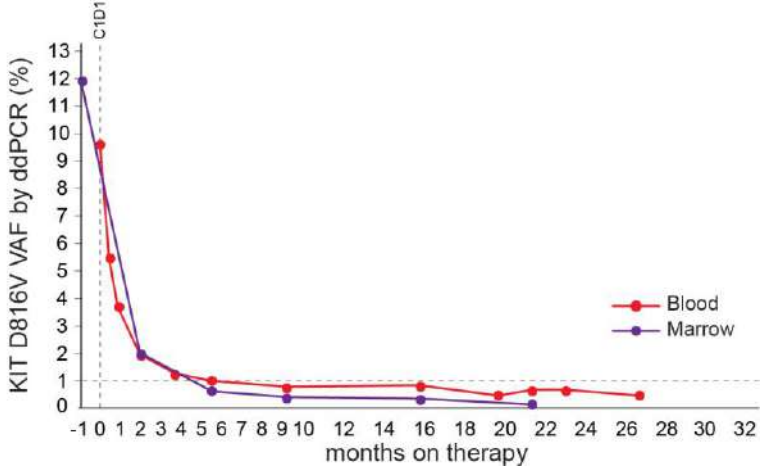
- Most AEs were grade 1 or 2
- Cytopenias were most common ≥ grade 3 treatment-related AE
- No grade 5 treatment-related AEs

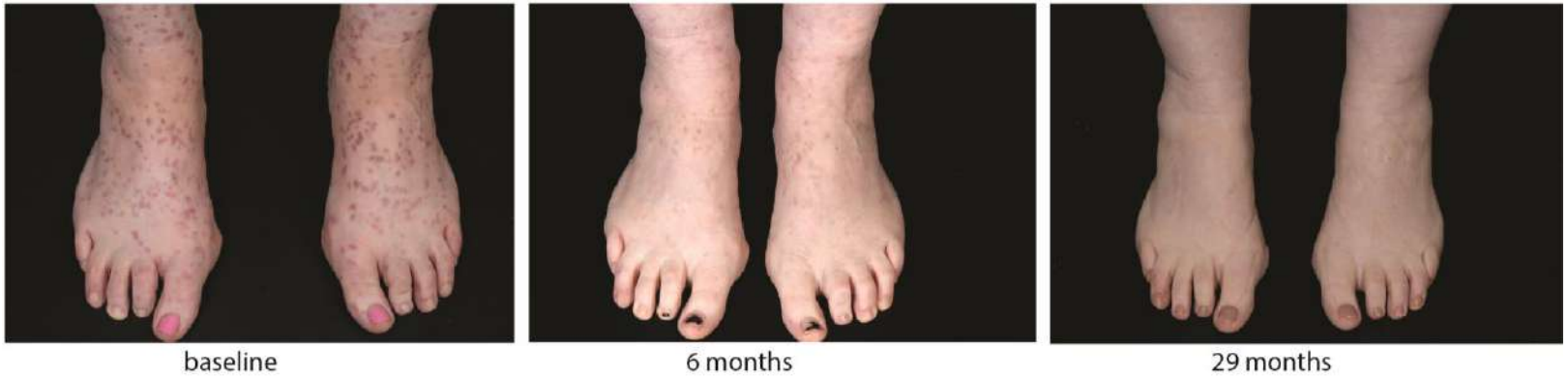
- 4% (3/69) discontinued due to treatment-related AEs
  - Refractory ascites, encephalopathy and ICB
- 13% (9/69) discontinued due to clinical progression
  - 3 AMLs, 3 AHNs, 3 SM
- Intracranial bleeding (ICB) occurred in 7 patients**
  - 5 of 7 patients resumed therapy
  - No new ICB events reported since implementing dose modifications for thrombocytopenia
- 71% (49/69) remain on treatment

AEs of note: ascites (n=6 [9%]; n=1 [1%] at ≥ grade 3), pleural effusion (n=9 [13%], n= 1[1%] at ≥ grade 3)
*Cognitive effects include: cognitive disorder, confusional state, memory impairment and encephalopathy
**1 ICB was in setting of severe head trauma

45yo woman with SM-AHN (MDS/MPN-U)







baseline | 6 months | 29 months

Patient permission granted for use of photos

Avapritinib induces complete and durable responses across SM spectrum

- **77% confirmed central ORR by mIWG-MRT-ECNM criteria in AdvSM**
  - Responses across all subtypes and poor prognosis S/A/R genotype
- **Responses occur at a median time of 2 mos and deepen over time**
  - Dose escalation patients (even cohort 1) still on therapy up to 34 months
  - KIT D816V eventually becomes undetectable in the marrow in 33% of patients
- **Only 4% discontinued for related AEs and 71% remain on treatment**
  - Starting dose of 200mg QD and platelet dose modifications implemented to improve long term safety and tolerability
- Granted Breakthrough Designation for AdvSM and Orphan Designation for Mastocytosis
- Phase 2 trials for AdvSM and ISM/SSM are enrolling in Europe and North America

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Patients & Families

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