

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

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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

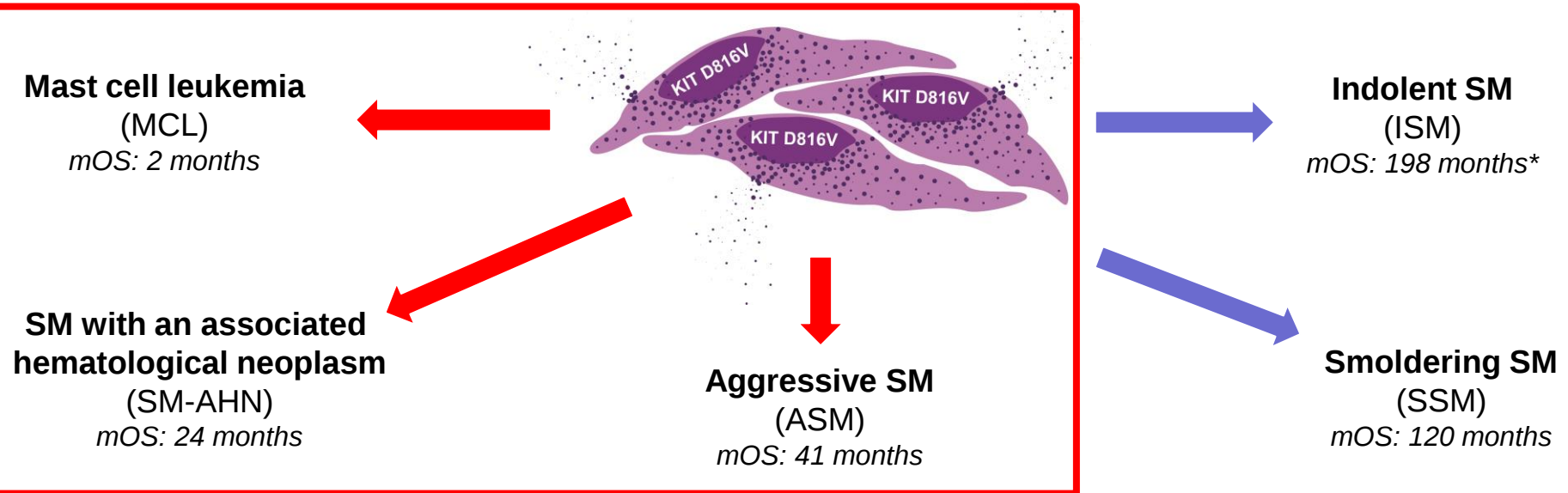
Speaker's Bureau: Novartis

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

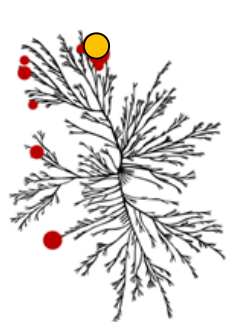
Systemic mastocytosis (SM) is a clonal mast cell disease

- *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 survival¹⁻³

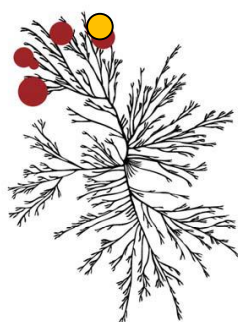
Advanced SM (AdvSM) – organ damage



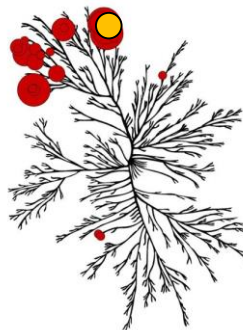
Avapritinib potently and selectively targets *KIT* D816V



avapritinib



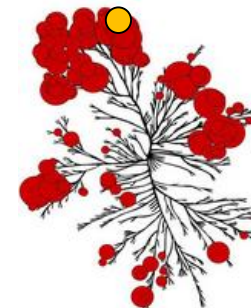
imatinib



masitinib



midostaurin



riporetinib

● Binding to KIT

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

KIT D816V biochemical IC₅₀

avapritinib*	imatinib*	masitinib [#]	midostaurin*	riporetinib [#]
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Biochemical binding by DiscoverRX at 3μM

*Evans EK et al. *Sci Transl Med.* 2017;9(414)

[#]Blueprint Medicines internal data on file

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Phase 1 EXPLORER clinical trial design

Part 1: Dose escalation (N=32)

avapritinib 30-400 mg QD

AdvSM or relapsed/refractory
myeloid malignancy

Part 2: Expansion (N=37)

Cohort 1: 300 mg QD

AdvSM

Cohort 2: 200 mg QD

AdvSM, mIWG-MRT-ECNM
evaluable

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 $\geq 25 \times 10^9/L$

Study objectives:

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

EXPLORER 
Advanced SM

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

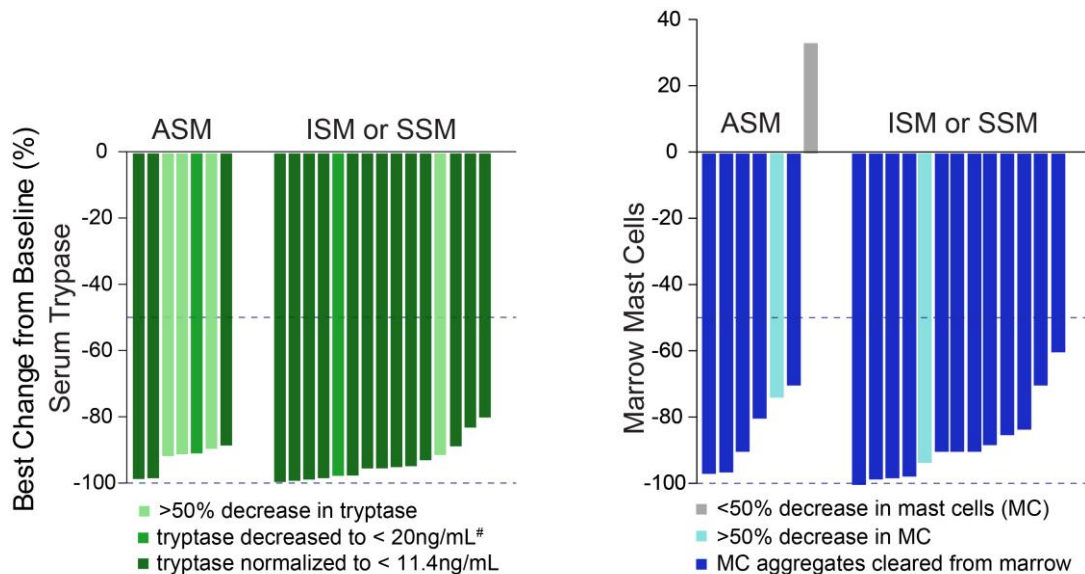
45% of local subtyping changed during central adjudication

1. Found AHN on central pathology (i.e., ASM $\rightarrow$ SM-AHN, 20%)
2. WHO C-findings not present/documented upon review (ie. ASM $\rightarrow$ 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

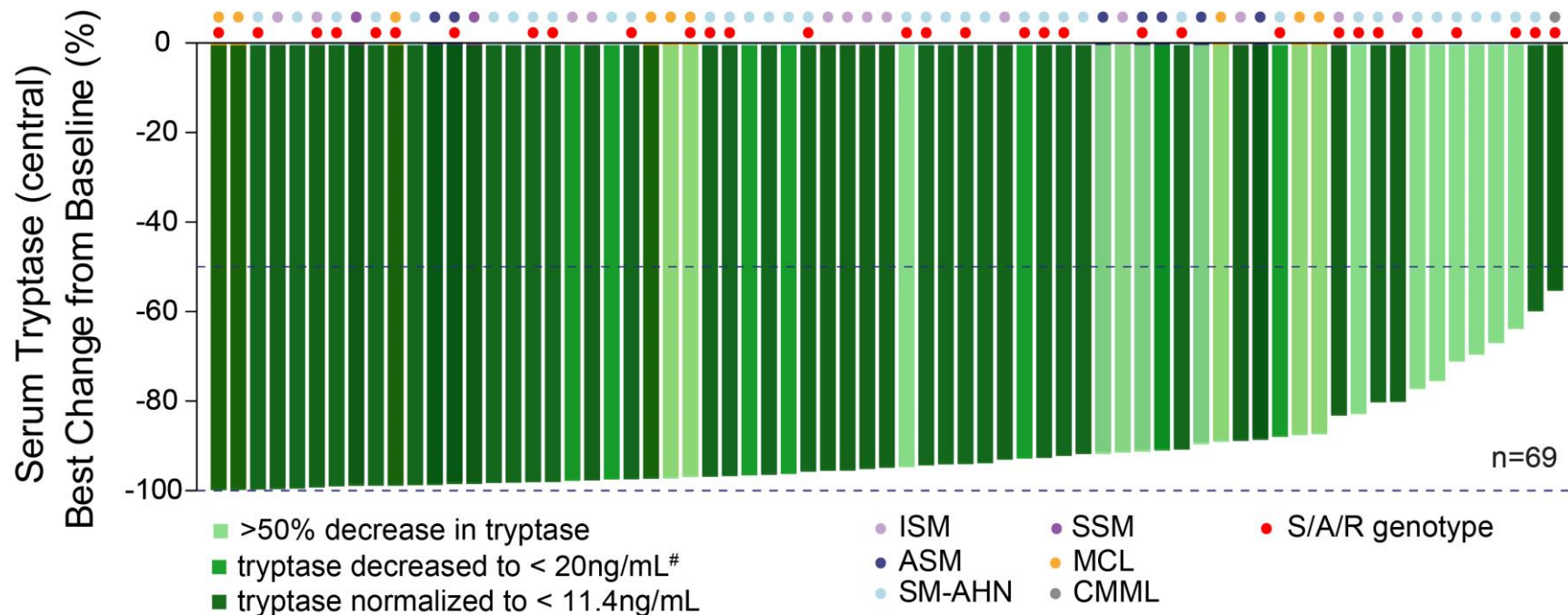
Baseline characteristics

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

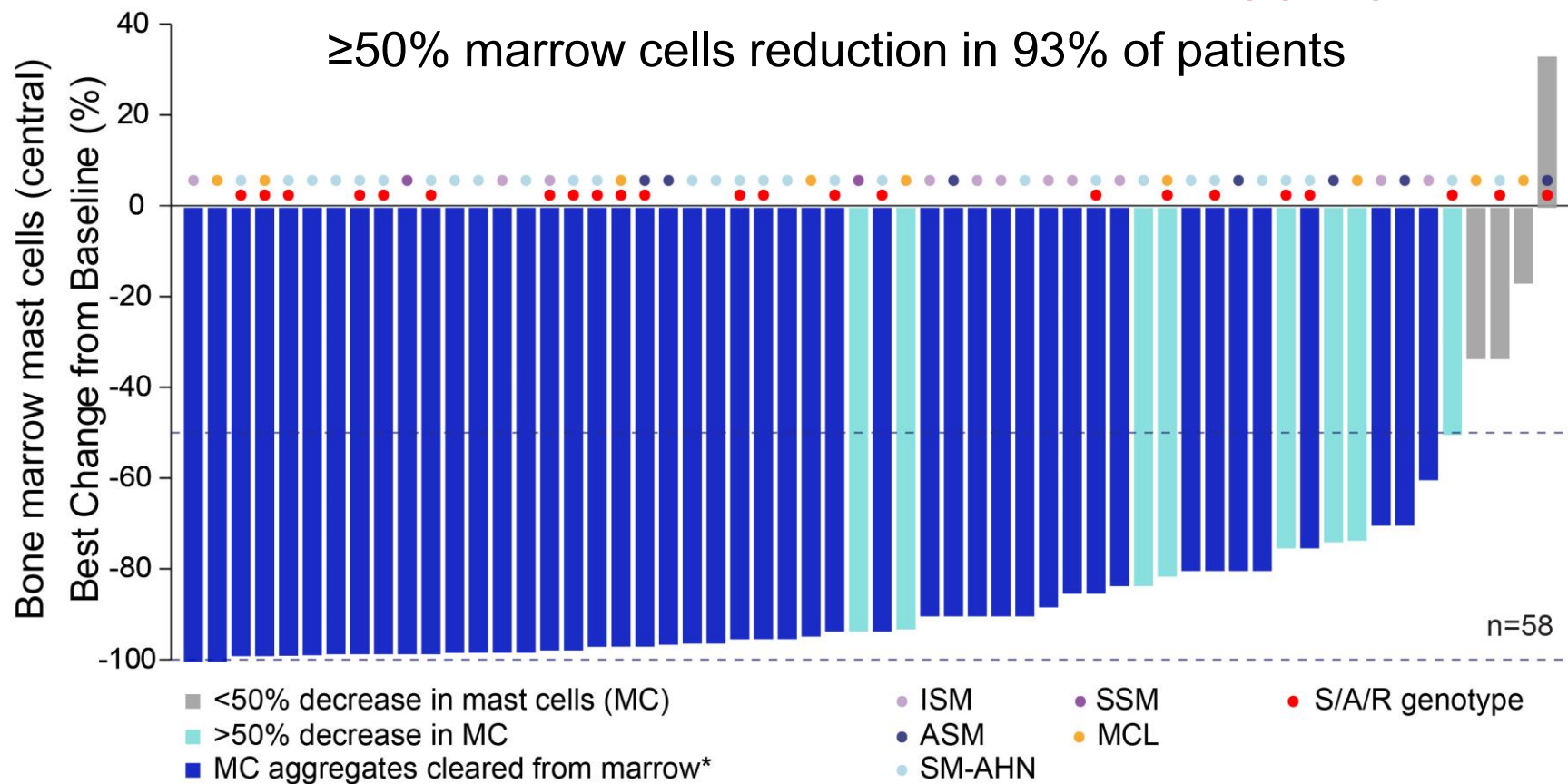


normal serum tryptase is defined as <11.4ng/mL

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

79% of patients clear marrow mast cell aggregates

≥50% marrow cells reduction in 93% of patients

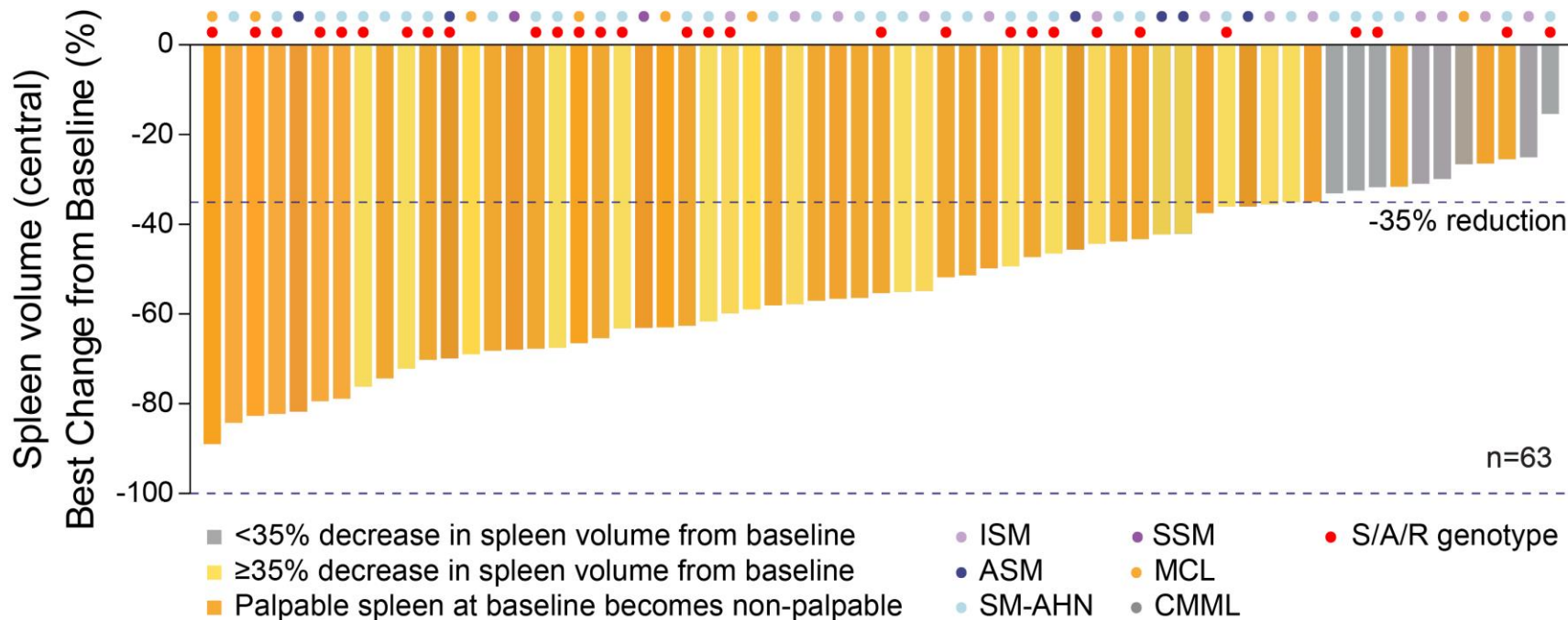


Only patients with MC aggregates at baseline who have post-baseline assessments included

* 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

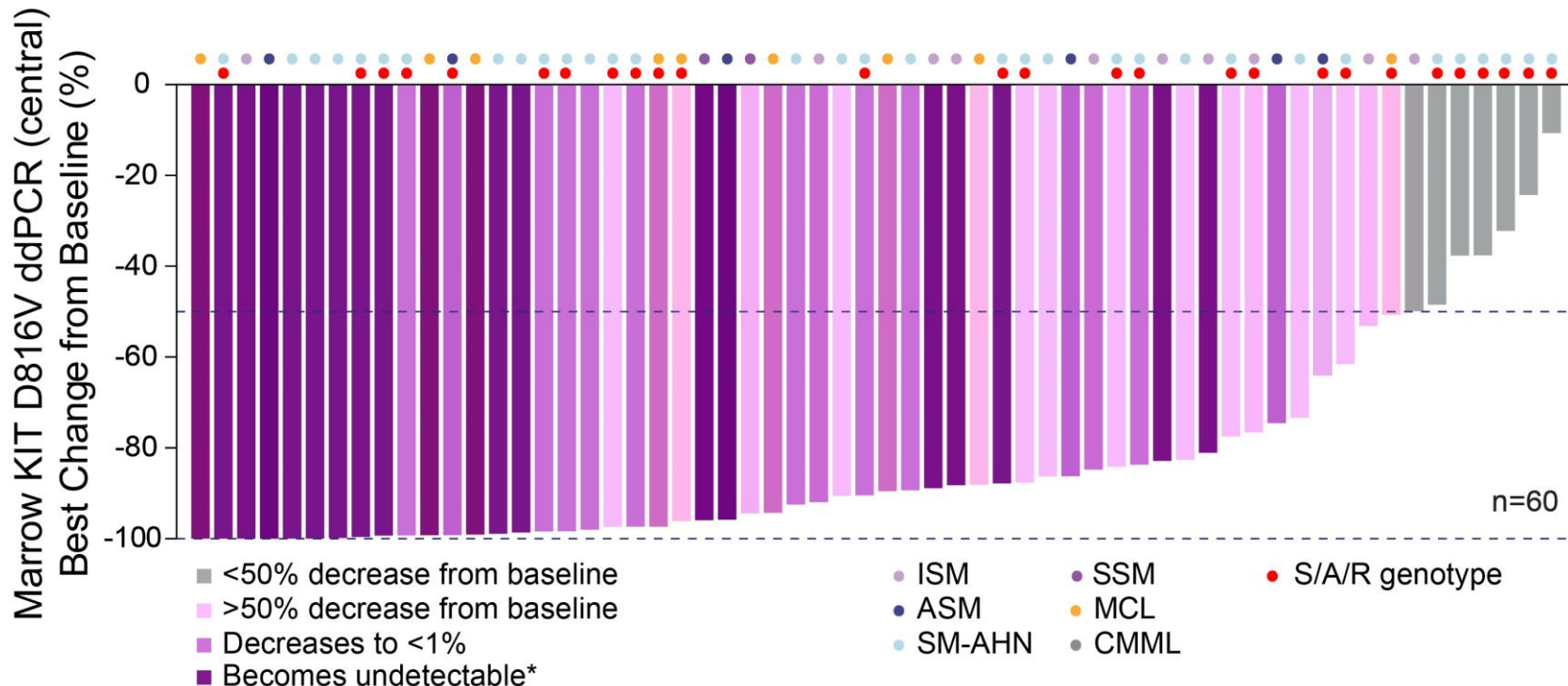


Only patients with measurable spleens at baseline who have post-baseline assessments included

*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



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

Best <u>confirmed</u> 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

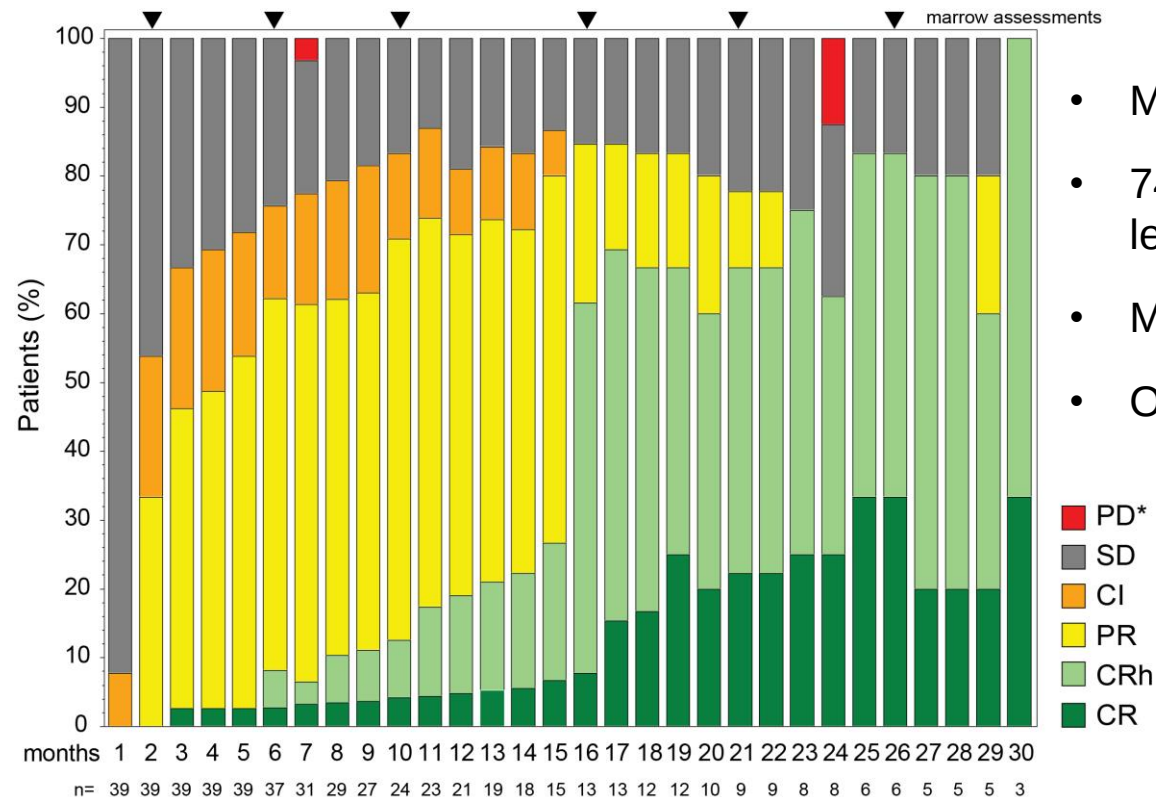
All responses (CR, CRh, PR, CI) confirmed at ≥12 weeks

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 × 10⁹/L with normal differential (absence of neoplastic MCs and blasts < 1%) and Platelet count > 50 × 10⁹/L and Hgb level > 8.0 g/dL

S/A/R: A poor prognosis SRSF2, ASXL1 or RUNX1 mutation detected at baseline

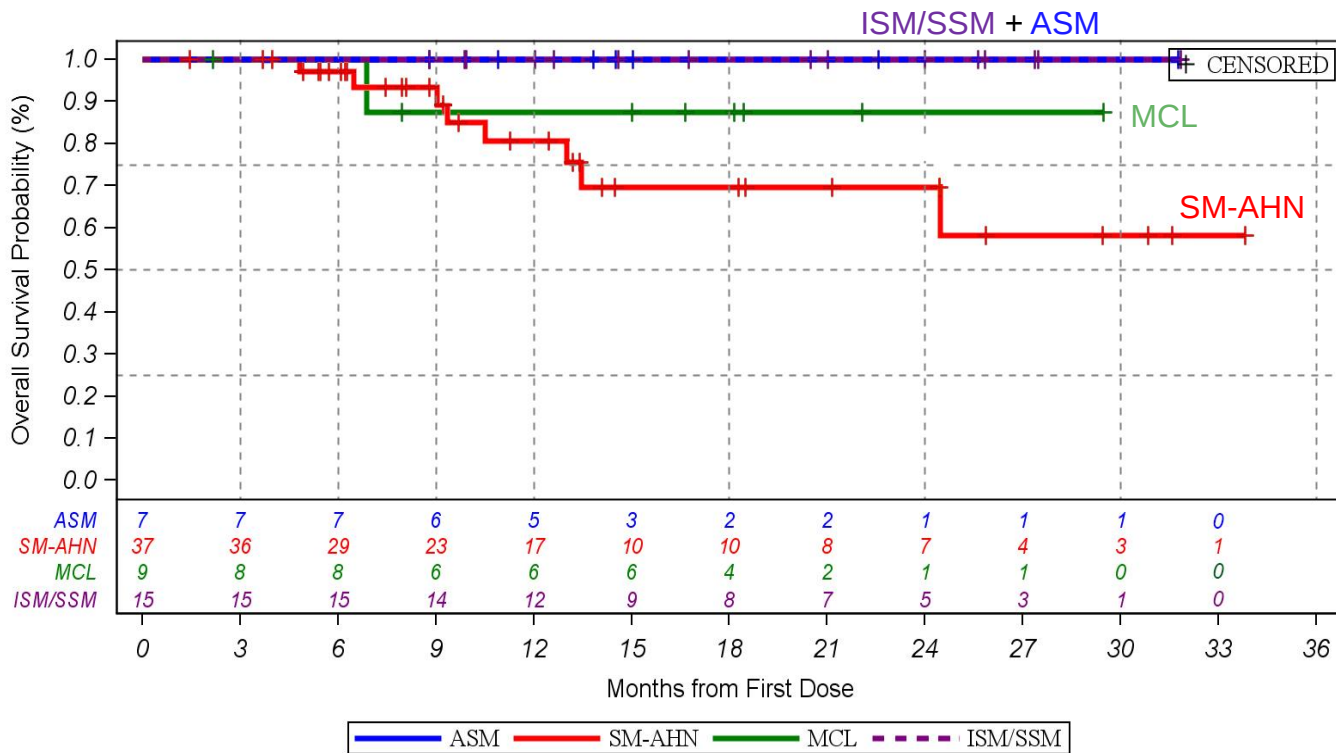
*No patients were primary progressors within the first 12 weeks

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

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

Treatment-emergent adverse events (AEs)

Adverse event, n (%)	Any Grade	Grade 3/4
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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)

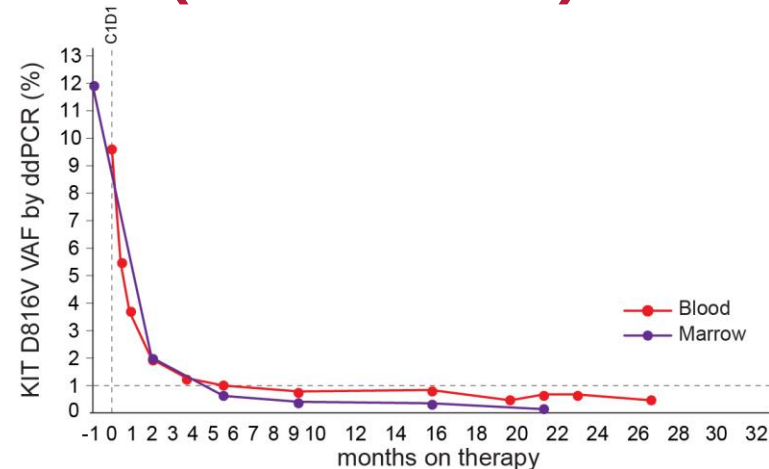
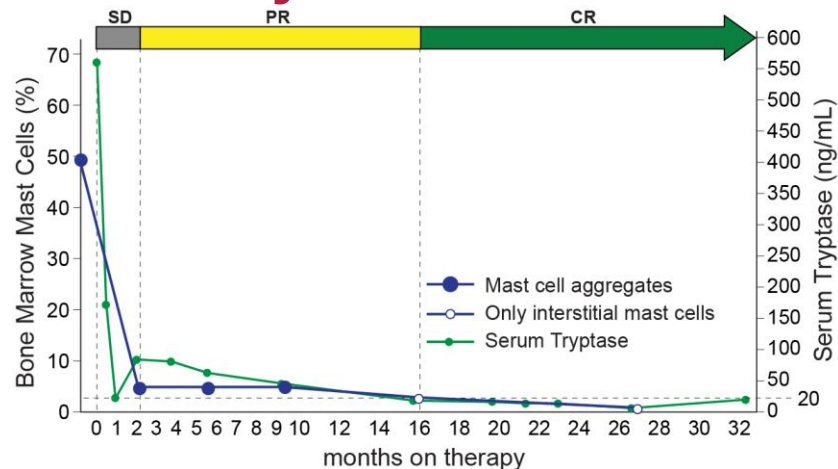
AEs of note: ascites (n=6 [9%]; n=1 [1%] at ≥ grade 3), pleural effusion (n=9 [13%], n= 1[1%] at ≥ grade 3)

*Cognitive effects include: cognitive disorder, confusional state, memory impairment and encephalopathy

**1 ICB was in setting of severe head trauma

- 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

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

EXPLORER 
Advanced SM