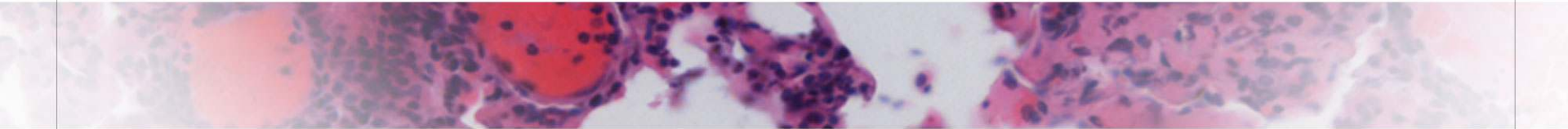




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A horizontal band showing a microscopic image of tissue, likely stained with hematoxylin and eosin (H&E), showing various cellular structures and colors.

Clinical activity in a Phase 1 study of BLU-285, a potent, highly-selective inhibitor of KIT D816V in advanced systemic mastocytosis

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Systemic mastocytosis (SM)

Diagnostic Criteria for systemic mastocytosis¹

WHO Criteria

•Major (+1 minor)

Mast cell aggregates (≥ 15) in BM or other tissue

•Minor (or 3 of 4)

Spindle-shaped mast cells
c-KIT D816V mutation present
CD2 or CD25 expression on mast cells
Serum tryptase > 20 ng/mL

KIT D816V drives systemic mastocytosis²⁻³

Indolent
(ISM)
16,100 cases[#]

Smoldering
(SSM)
1,800 cases[#]

Advanced
(AdvSM)
2,600 cases[#]

KIT D816V



Debilitating symptoms



Organ damage



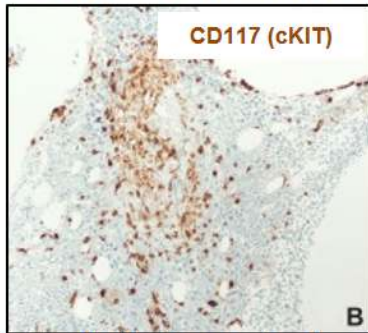
↓ Survival

[#]Represents estimated prevalence in US, EU5, Japan. WHO, World Health Organization; AdvSM, advanced SM; ISM, indolent SM; SSM, smoldering SM

Systemic mastocytosis (SM)

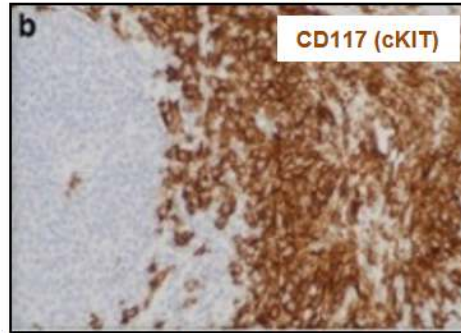
Advanced systemic mastocytosis *ASM, SM-AHN and MCL*

Bone and bone marrow*



Osteolytic bone lesions
Cytopenias

Liver and spleen†



Liver function abnormalities,
Ascites, or Hypersplenism

GI tract‡



Hypoalbuminemia
Weight loss

C-findings

*Represents estimated prevalence in US, EU5, Japan. AdvSM, advanced SM; ASM, aggressive systemic mastocytosis; GI, gastrointestinal; ISM, indolent SM; MC, mast cell; MCL, mast cell leukemia; SM-AHN, SM-associated hematologic neoplasm; SSM, smoldering SM. Images reproduced with permission from: *Metcalfe Blood (2008) 112:4; †Ammanagari N et al Ann Hematol (2013) 92:1573–1575; ‡Behdad A., Owens SR Arch Pathol Lab Med (2013) 137:1220–1223; §Hartmann K et al Journal of Allergy and Clinical Immunology (2016) 137 (1) 35–45

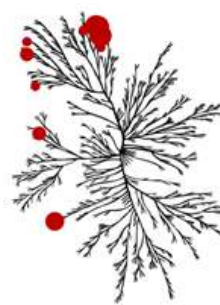
BLU-285 was designed to treat systemic mastocytosis

BLU-285 provides highly potent and selective targeting of KIT D816V¹

Biochemical IC₅₀ (nM)

	KIT D816V	KIT wild type
BLU-285	0.27	73
Midostaurin	2.9	26

Kinome selectivity*



BLU-285



Midostaurin

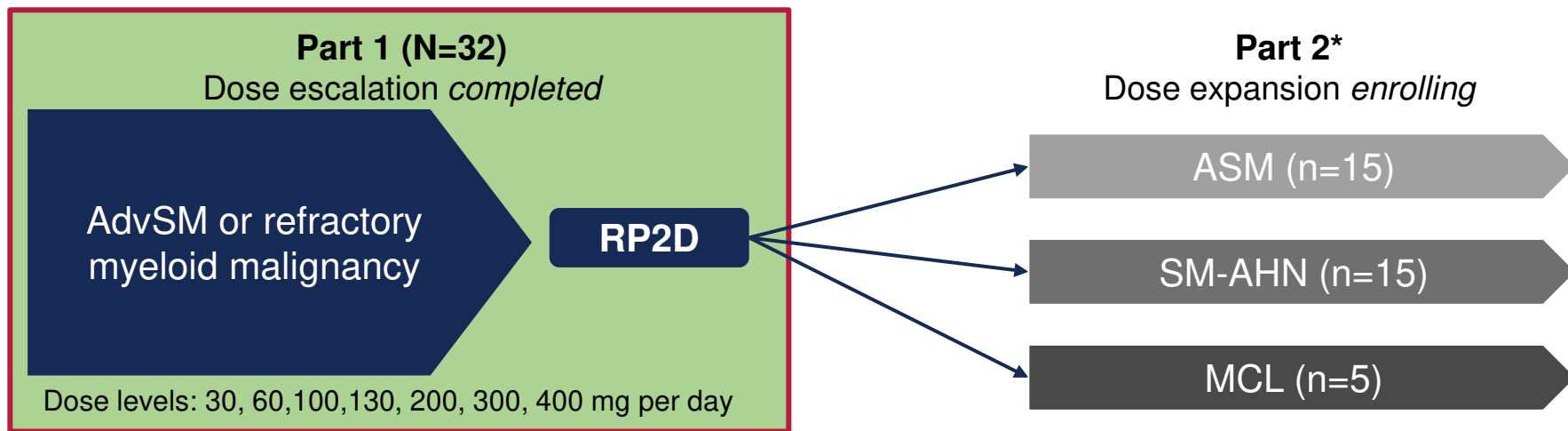
- Multikinase inhibitor midostaurin is the only approved treatment for AdvSM
- Midostaurin provides CR+PR of 17% per IWG-MRT-ECNM criteria;² mPFS 14.1 months³

*Reproduced courtesy of Cell Signalling Technology, Inc. (www.cellsignal.com). The website is maintained by CSTI, Blueprint Medicines is not responsible for its content. IC₅₀, concentration causing 50% inhibition; CR, complete response; PR, partial response; IWG-MRT-ECNM, International Working Group-Myeloproliferative Neoplasms Research and Treatment & European Competence Network on Mastocytosis; mPFS, median progression free survival

Phase 1 study of BLU-285 in advanced systemic mastocytosis: study design

Primary objectives: MTD/RP2D and safety profile

Secondary objectives: pharmacokinetics and preliminary anti-tumor activity



BLU-285 continuous oral once-daily dosing

*As of November 27, 2017, 7 patients have been enrolled in dose expansion (data not shown); MTD, maximum tolerated dose; RP2D, recommended Part 2 dose

Key entry criteria

- Disease entities:
 - Advanced systemic mastocytosis per WHO diagnostic criteria via local assessment:
 - One of the following three histologic subtypes:
 - Aggressive systemic mastocytosis
 - Systemic mastocytosis with associated hematologic neoplasm with ≥ 1 C-finding
 - Mast cell leukemia
 - Relapsed or refractory myeloid malignancy (dose escalation only)
- Age ≥ 18 years
- ECOG performance status 0–3
- Platelet count $\geq 25 \times 10^9$ /L
- ANC $\geq 0.5 \times 10^9$ /L
- Adequate hepatic and renal function

WHO Criteria for SM

- **Major**
 - Mast cell aggregates (≥ 15) in BM or other tissue
- **Minor**
 - Spindle-shaped mast cells
 - c-KIT D816V mutation present
 - CD2 or CD25 expression on mast cells
 - Serum tryptase > 20 ng/mL

ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group.

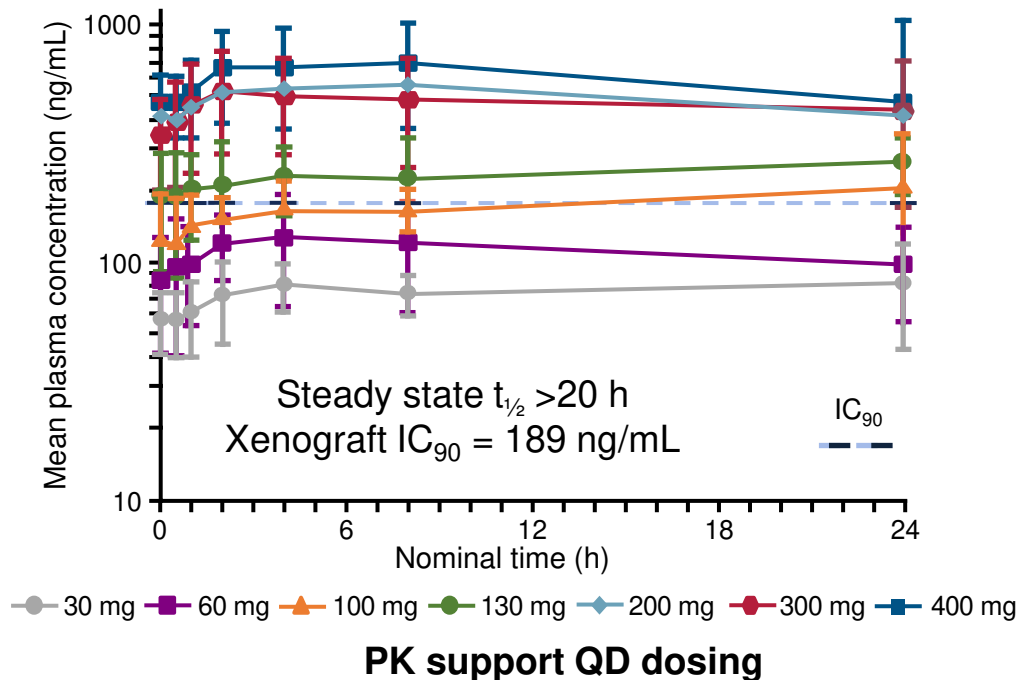
Baseline characteristics

Parameter		All patients (N=32)
Median age, years (range)		63 (34–83)
Disease subtype per local assessment, n (%) [*]	ASM	17 (53)
	SM-AHN	9 (28)
	MCL	3 (9)
<i>KIT</i> mutation, n (%)	D816V	28 (88)
High risk mutation positive, ^{1,2} n (%)	Any (<i>SRSF2</i> , <i>ASXL1</i> or <i>RUNX1</i>) [#]	14 (44)
ECOG performance status, n (%)	0-1	27 (84)
	2	5 (16)
Prior anti-neoplastic therapy	Median number (range)	1 (0-2)
	Any, n (%)	22 [^] (69)
	Midostaurin	4 (13)
C-findings per WHO Criteria	Median number (range)	1 (0–4)
	Cytopenias, n (%)	17 (53)
	Hepatomegaly with liver dysfunction	5 (16)
	Hypersplenism	11 (34)
	Malabsorption with weight loss	9 (28)
	Osteolytic bone lesions	6 (19)

^{*}Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1); [#]Patients could have more than one S/A/R gene mutated, *SFSR2* (n=22), *ASXL1* (n=7), *RUNX1* (n=5). S/A/R, mutations potentially associated with a poorer prognosis^{1,2}; [^]Prior therapy taken by ≥2 pts, cladribine (n=6), imatinib (n=4), interferon (n=4), midostaurin (n=4), azacitidine (n=3), hydroxyurea (n=2), ibrutinib (n=2)

BLU-285 pharmacokinetics (PK) and dose escalation cohorts

Steady state PK



QD, once daily; DLT, dose-limiting toxicity

3+3 dose escalation with enrichment

Dose (mg)	Patients (n)	DLT (n)
30	3	0
60	6	1 Grade 3 alk phos
100	3	0
130	3	0
200	4	0
300	6	0
400	7	1 Grade 4 vomiting

MTD not reached
300 mg daily selected as the RP2D

Treatment-emergent adverse events

NON-HEMATOLOGICAL AEs ≥20% (N=32)

Adverse event, n (%)	Any grade	≥Grade 3
Periorbital edema	19 (59)	2 (6)
Fatigue	13 (41)	2 (6)
Peripheral edema	11 (34)	0
Nausea	9 (28)	1 (3)
Abdominal pain	7 (22)	0
Diarrhea	7 (22)	1 (3)
Respiratory tract infection	7 (22)	0
Dizziness	7 (22)	0
Headache	7 (22)	0

HEMATOLOGICAL AEs ≥10% (N=32)

Anemia	9 (28)	3 (9)
Thrombocytopenia	9 (28)	2 (6)
Neutropenia	4 (13)	4 (13)

Most adverse events were
CTCAE grade 1 or 2

≥ Grade 3 treatment-related AE in 16 (50%) patients
No deaths on study

30 of 32
patients remain on treatment
(Median 9 months [range: 4–19])

1 discontinued
due to PD (AML)

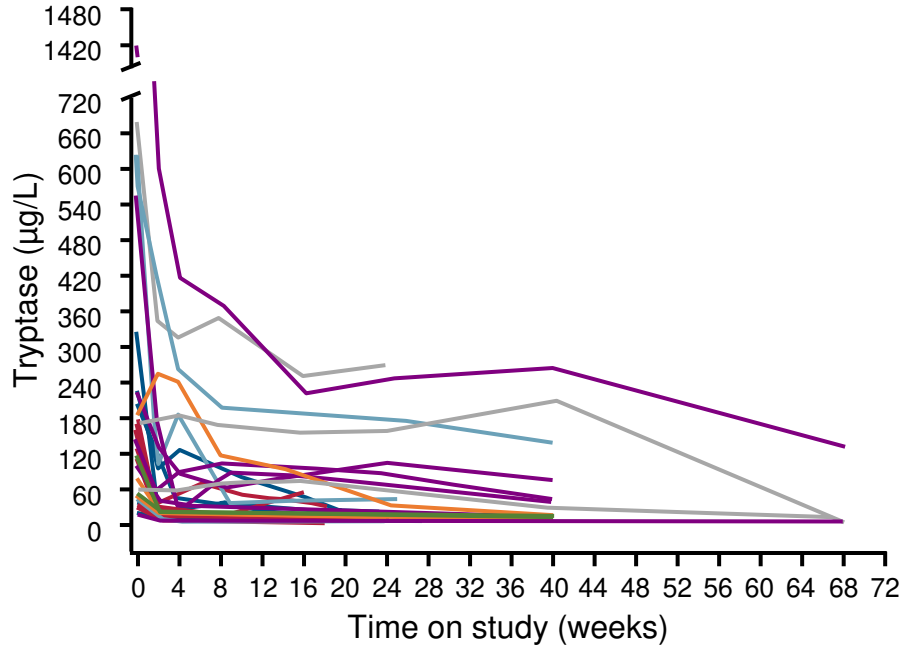
1 investigator decision
(wild type *KIT*)

***None discontinued due to
BLU-285-related AE***

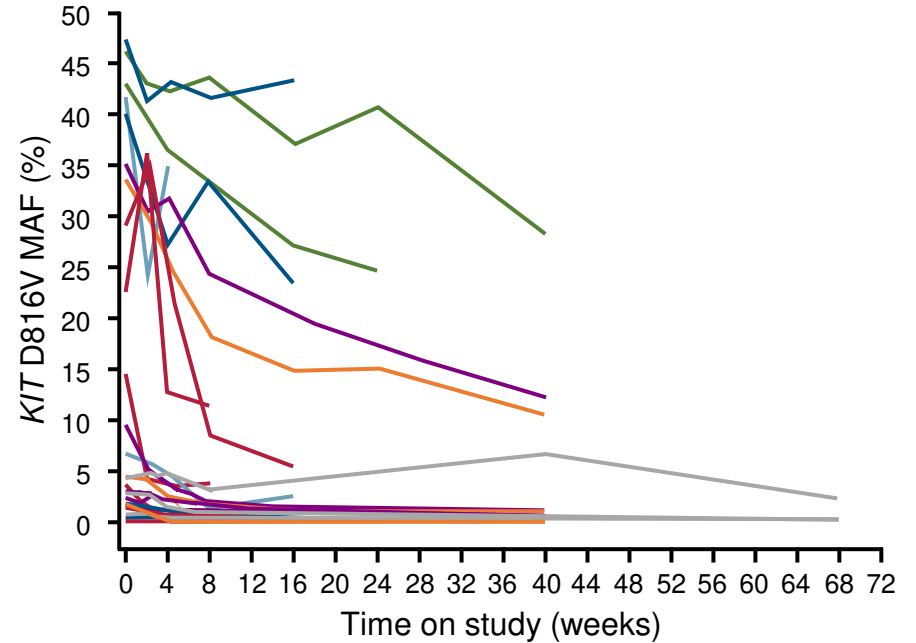
AE, adverse event; AML, acute myeloid leukemia; CTCAE, Common Terminology Criteria for Adverse Events; PD, progressive disease

Rapid and durable decline in tryptase and *KIT* D816V variant allele fraction across all dose levels

Serum tryptase



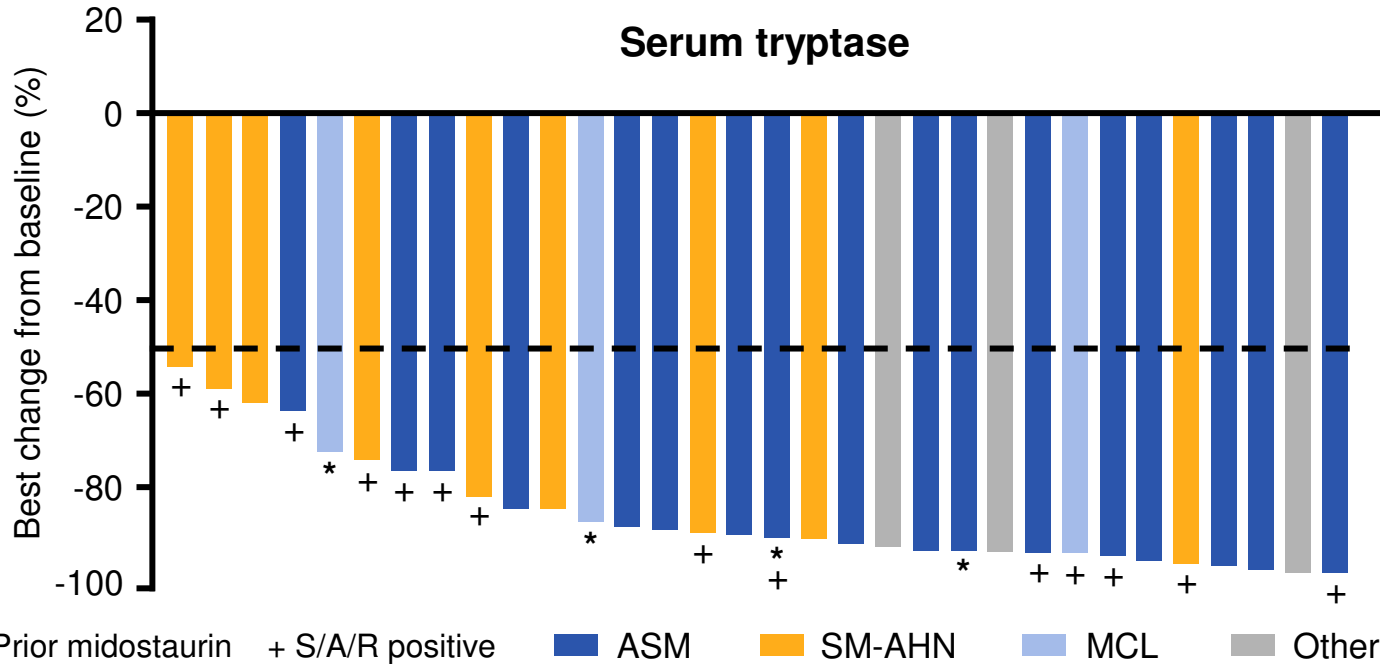
Blood *KIT* D816V VAF



Dose mg — 30 mg — 100 mg — 200 mg — 400 mg
 — 60 mg — 130 mg — 300 mg

MAF, mutant allele fraction

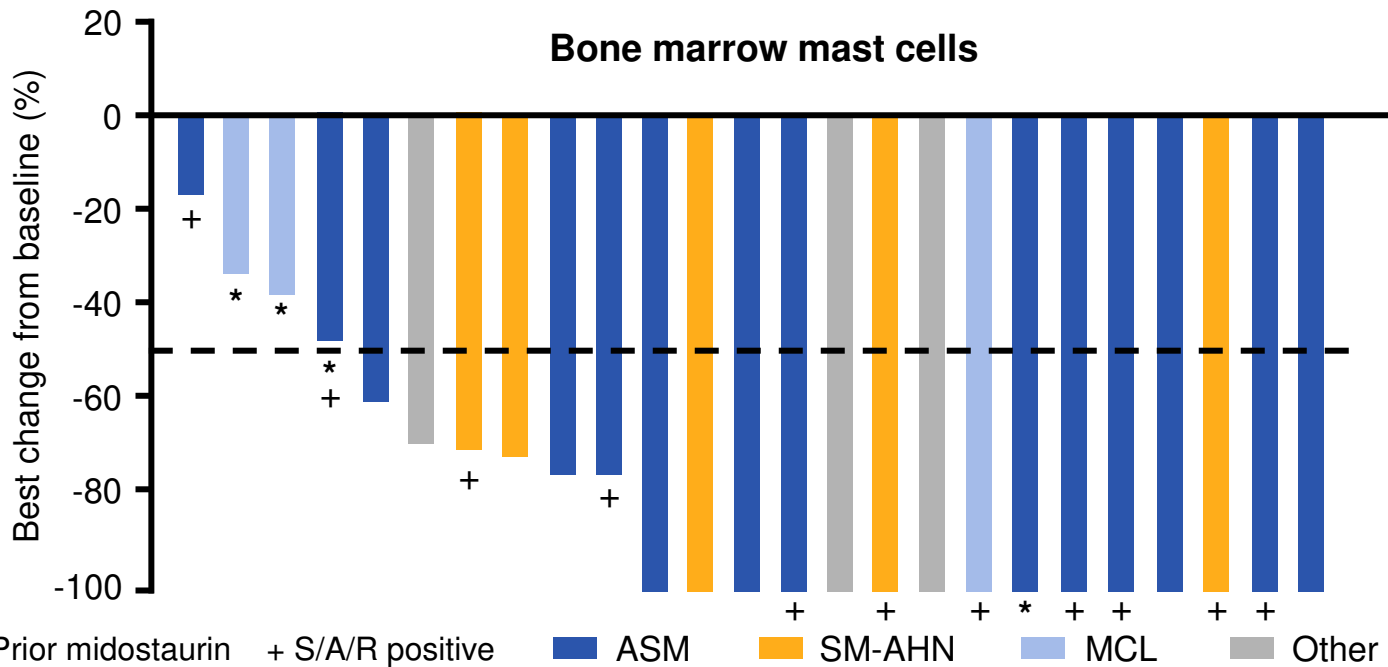
Tryptase decrease in all patients



- Baseline median 124 $\mu\text{g/L}$, range 14 to 1414 $\mu\text{g/L}$
- All 32 patients achieved >50% reduction from baseline

Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1)

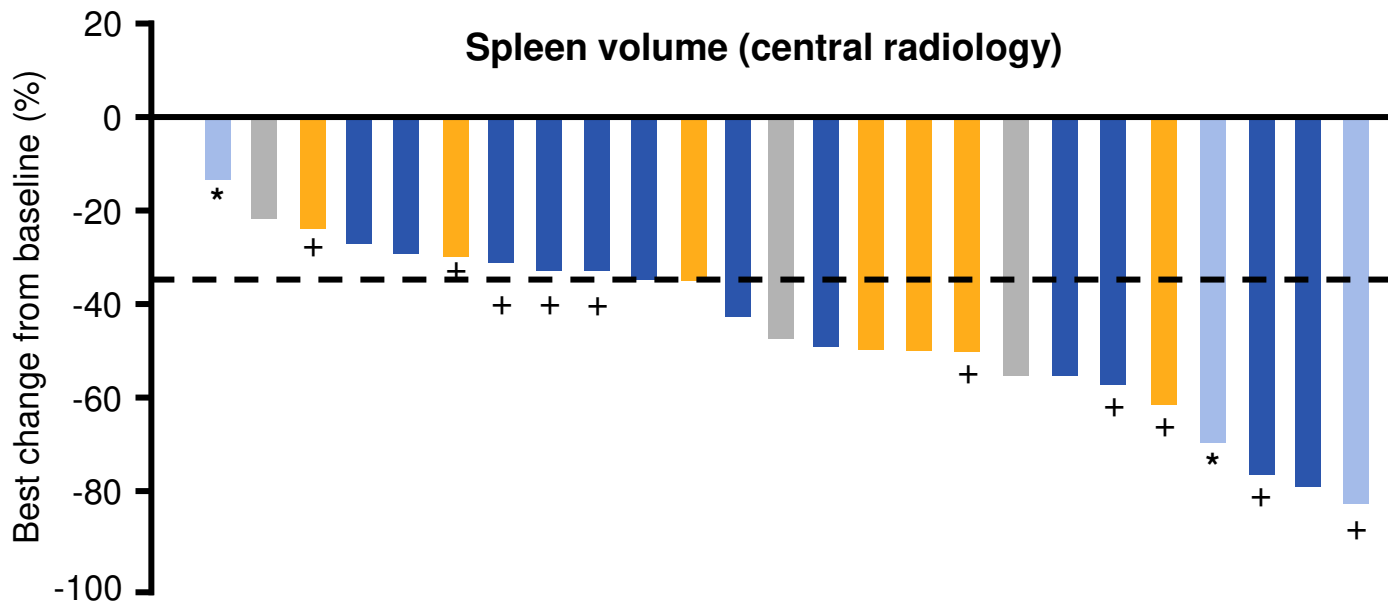
Bone marrow mast cell decrease in all patients[^]



- Baseline median 20%, range 1.5 to 95%
- [^]n=25 evaluable patients with baseline bone marrow mast cells ≥ 5%
- 15/25 (60%) patients achieved bone marrow CR

Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1)

Spleen volume decrease in all patients[^]



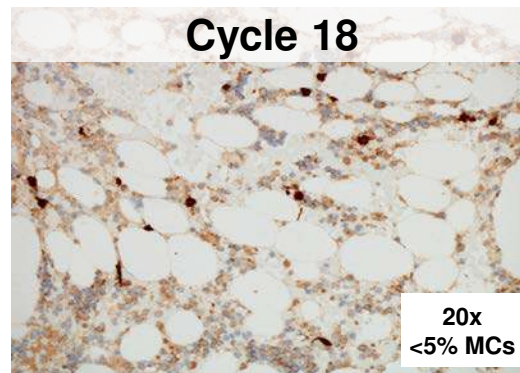
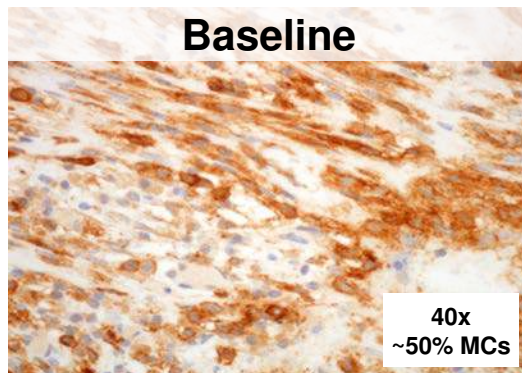
* Prior midostaurin + S/A/R positive ■ ASM ■ SM-AHN ■ MCL ■ Other

- Baseline median 633 mL, range 130 to 1952 mL
- [^]n=25 patients with splenomegaly as per central assessment
- 15/25 (60%) patients achieved >35% reduction of spleen volume

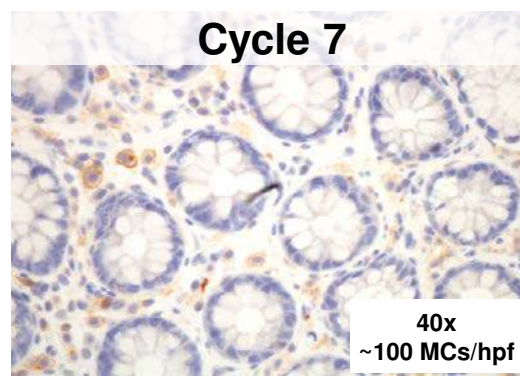
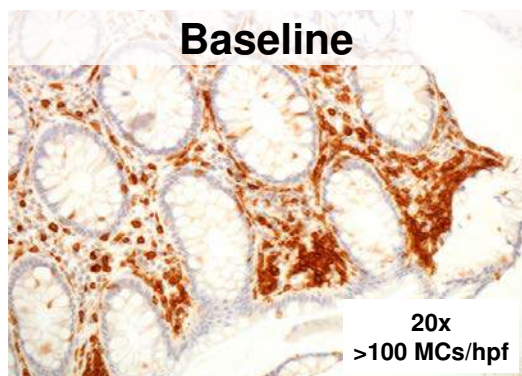
Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1)

45-year-old female with ASM

Bone marrow
tryptase



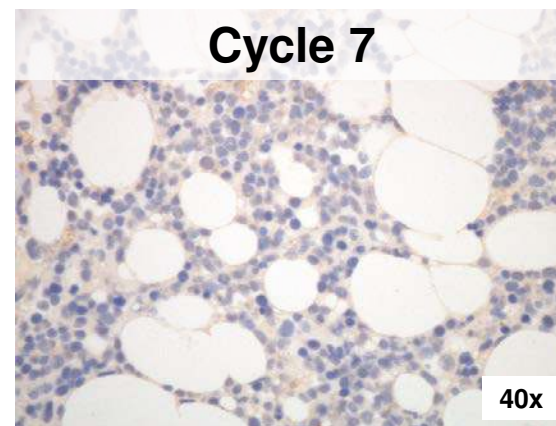
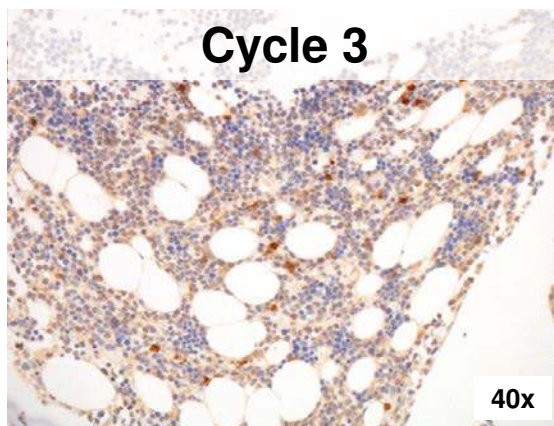
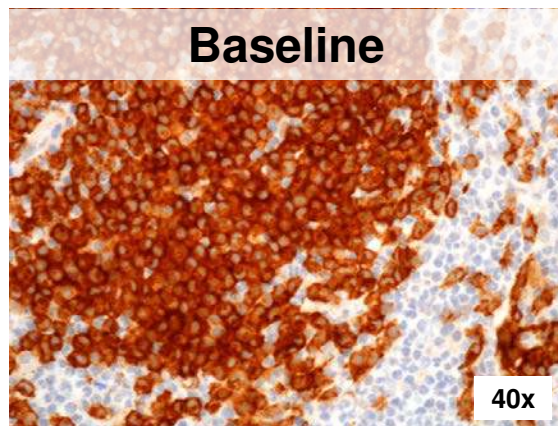
Colon
CD25



*BLU-285 60 mg; remains on treatment at cycle 18 with confirmed PR per IWG-MRT-ECNM

64-year-old male with MCL

Progressive clearance of bone marrow mast cells



Bone marrow CD117

*BLU-285 200 mg; remains on treatment at cycle 9 with confirmed PR per IWG-MRT-ECNM

Response analysis per IWG-MRT-ECNM criteria

Complete response (CR)¹

- No bone marrow mast cell aggregate
- Serum tryptase <20 ng/mL
- Peripheral blood count remission
- Complete resolution of C-findings

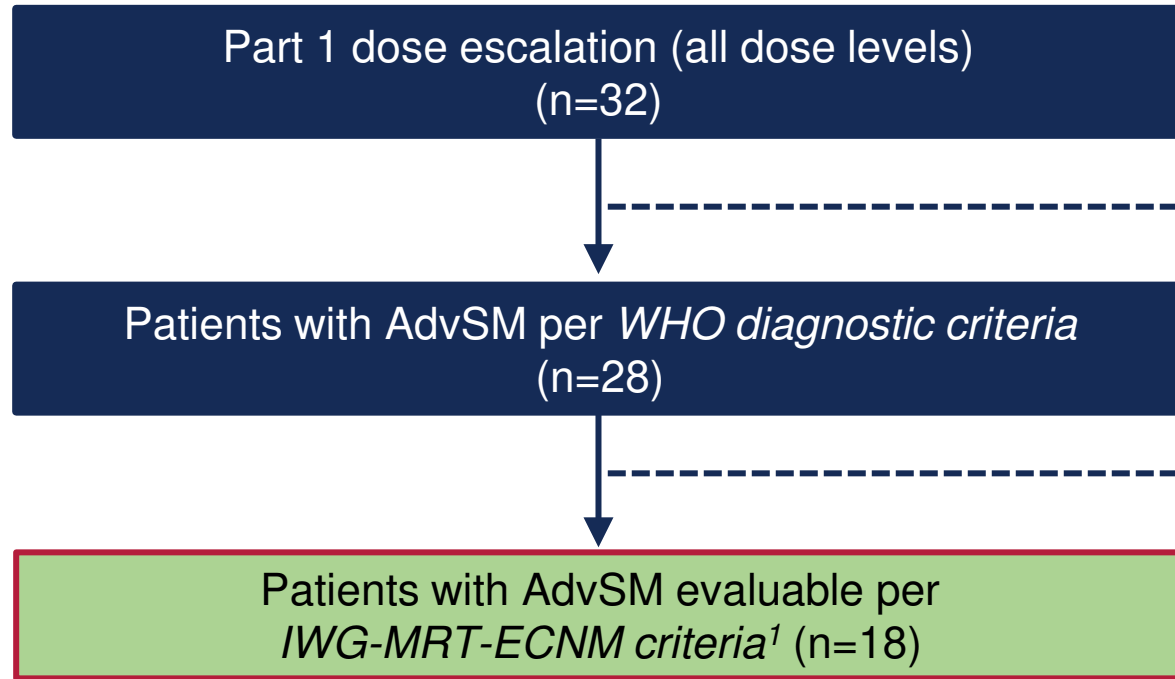
Partial response (PR)¹

- ≥50% reduction in bone marrow mast cell aggregate
- ≥50% reduction in serum tryptase
- Resolution of 1 or more C-findings

Clinical improvement (CI)¹

- 1 or more response criteria in absence of CR, PR or PD

IWG-MRT-ECNM evaluable patients



Patients inevaluable (n=4)

- n=3 non-SM myeloid malignancy
- n=1 *KIT* WT; discontinued prior to post baseline response assessment

Patients excluded (n=10)

- n=6 only had osteolytic bone disease at baseline
- n=4 not measurable per IWG-MRT-ECNM criteria at baseline

WT, wild type; 1. Gotlib J et al Blood (2013) 121:2393

Best overall response per IWG-MRT-ECNM criteria¹

Best response* n (%) (confirmed and unconfirmed)	ASM (n=7)	SM-AHN# (n=8)	MCL (n=3)	Overall (n=18)
Overall response rate (CR + PR + CI)	6 (86)	5 (63)	2 (67)	13 (72)
CR + PR	5 (71)	4 (50)	1 (33)	10 (56)
Complete response (CR)	2 (29)	0	0	2 (11)
Partial response (PR)	3 (43)	4 (50)	1 (33)	8 (44)
Clinical improvement (CI)	1 (14)	1 (13)	1 (33)	3 (17)
Stable disease (SD)	1 (14)	3 (38)	1 (33)	5 (28)
Progressive disease (PD)	0	0	0	0

- 17 of 18 patients remain on treatment with median duration 9 months (range: 4–19)

*Pending confirmation: ASM, 2 CR; SM-AHN, 3 PR; #Mastocytosis response; 1. Gotlib J et al Blood (2013) 121:2393

BLU-285 has potent, clinically important activity in AdvSM

- Data validate *KIT* D816V as a key disease driver
- Selective targeting of *KIT* D816V with BLU-285 is well tolerated
 - 30 of 32 patients remain on treatment with median duration of 9 months (range: 4–19)
 - RP2D is 300 mg once daily, and expansion is ongoing
- BLU-285 demonstrates high preliminary response rates and durable activity
 - 72% ORR (CR + PR + CI) with 56% CR + PR per IWG-MRT-ECNM criteria
- Additional clinical development with BLU-285, now avapritinib, across the spectrum of systemic mastocytosis is planned for 2018
 - Phase 2 trial in AdvSM
 - Dose finding and Phase 2 trial in ISM and SSM

Acknowledgments

- We thank the participating patients, their families, all study co-investigators, and research coordinators at the following institutions:
 - Deepti Radia, Guy's & St Thomas NHS Trust
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