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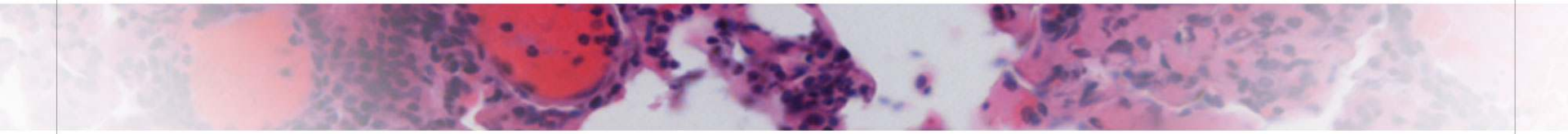

Clinical activity in a Phase 1 study of BLU-285, a potent, highly-selective inhibitor of KIT D816V in advanced systemic mastocytosis

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American Society of Hematology Annual Meeting, Atlanta, GA USA,10 Dec 2017

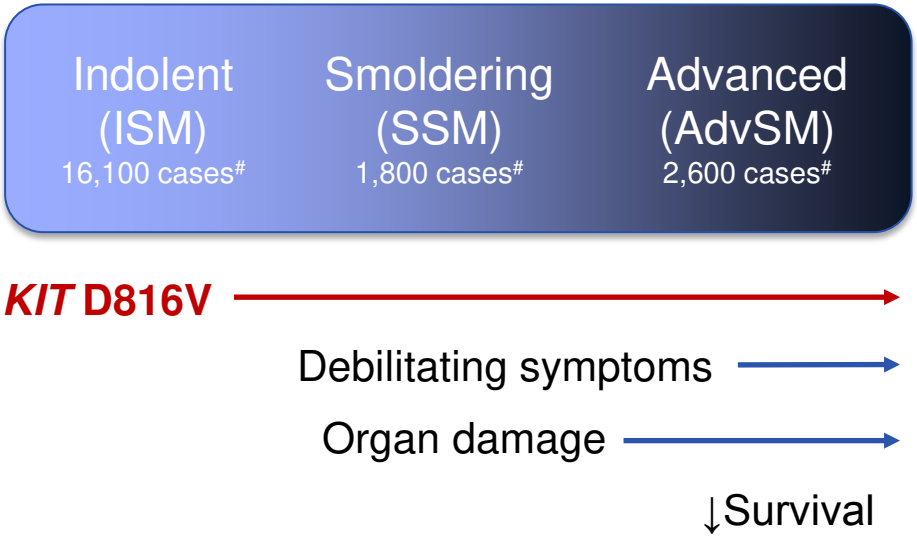
Systemic mastocytosis (SM)

***Diagnostic Criteria for* systemic mastocytosis[1]**

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 mastocytosis[2–3]**



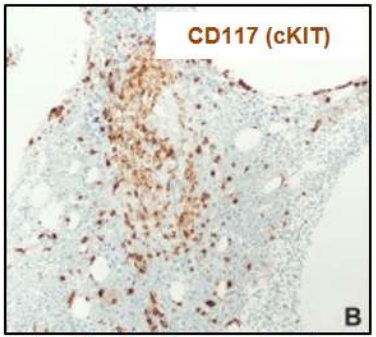
#Represents estimated prevalence in US, EU5, Japan. WHO, World Health Organization; AdvSM, advanced SM; ISM, indolent SM; SSM, smoldering SM

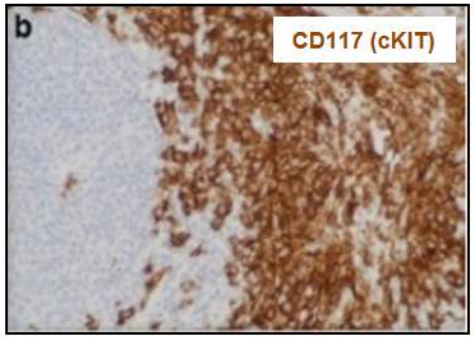
1. Arber DA, et al. Blood. 2016:127(20);2391-2405; 2. Valent P et al Cancer Res (2017) 77:1261;
3. Cohen S et al Br J Haematol (2014) 166(4):521-8 and World Bank Population estimates

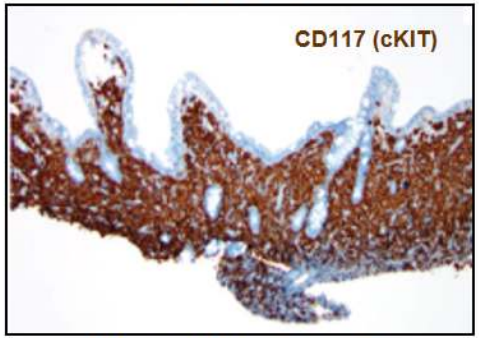
Systemic mastocytosis (SM)

Advanced systemic mastocytosis
ASM, SM-AHN and MCL

Bone and bone marrow* **Liver and spleen†** **GI tract‡**







Osteolytic bone lesions
Cytopenias

Liver function abnormalities,
Ascites, or Hypersplenism

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

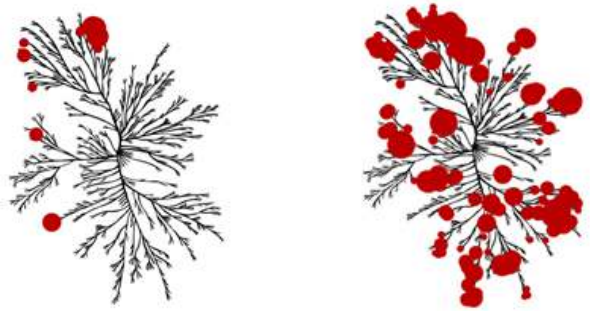
BLU-285 was designed to treat systemic mastocytosis

BLU-285 provides highly potent and selective targeting of KIT D816V[1]

Biochemical IC_{50} (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 months[3]

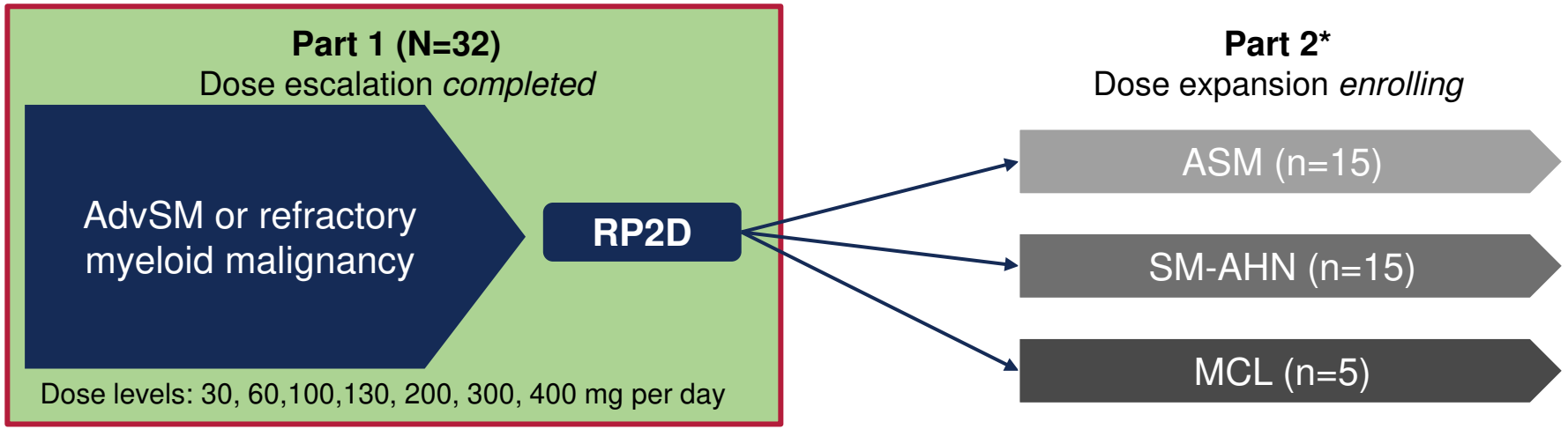
*Reproduced courtesy of Cell Signalling Technology, Inc. (www.cellsignal.com). The website is maintained by CSTI, Blueprint Medicines is not responsible for its content. IC_{50}, concentration causing 50% inhibition; CR, complete response; PR, partial response; IWG-MRT-ECNM, International Working Group-Myeloproliferative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

1. Evans E et al Science Translational Medicine (2017) 1;9(414);
2. Midostaurin US Prescribing information;
3. Gotlib J et al NEJM (2016) 374:2530

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 ≥ 25 x 10^9 /L
- ANC ≥ 0.5 x 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 SM-AHN MCL	17 (53) 9 (28) 3 (9)
KIT mutation, n (%)	D816V	28 (88)
High risk mutation positive,[1,2] n (%)	Any (*SRSF2*, *ASXL1* or *RUNX1*)[#]	14 (44)
ECOG performance status, n (%)	0-1 2	27 (84) 5 (16)
Prior anti-neoplastic therapy	Median number (range) Any, n (%) Midostaurin	1 (0-2) 22[^] (69) 4 (13)
C-findings per WHO Criteria	Median number (range) Cytopenias, n (%) Hepatomegaly with liver dysfunction Hypersplenism Malabsorption with weight loss Osteolytic bone lesions	1 (0–4) 17 (53) 5 (16) 11 (34) 9 (28) 6 (19)

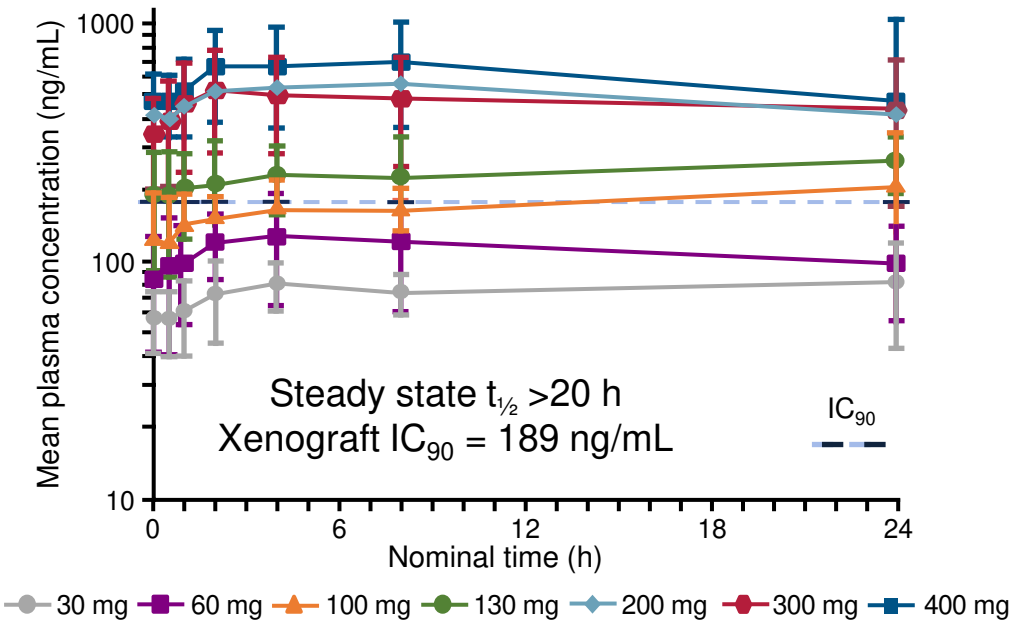
*Other, SSM (n=2); telangiectasia macularis eruptive perstans (n=1); [#] Patients could have more than one S/A/R gene mutated, *SFSR2 (n=22), ASXL1 (n=7), RUNX1 (n=5).* S/A/R, mutations potentially associated with a poorer prognosis[1,2]; [^] Prior therapy taken by ≥2 pts, cladribine (n=6), imatinib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

Data cut-off: 4 Oct 2017

1. Schwaab J et al Blood (2013) 122:2460;
2. Jawhar M et al Blood (2017) 130:137

BLU-285 pharmacokinetics (PK) and dose escalation cohorts

Steady state PK



PK support QD dosing

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

QD, once daily; DLT, dose-limiting toxicity

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)

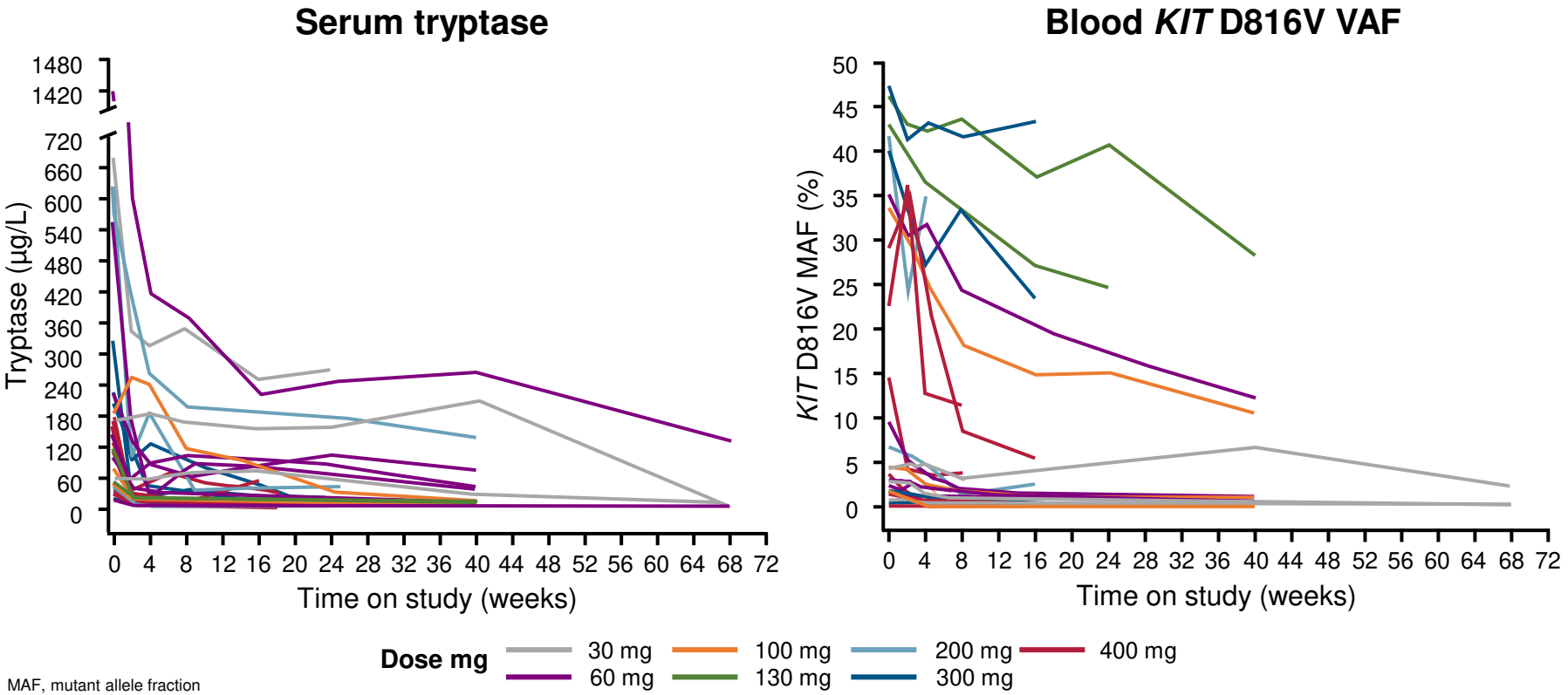
1 investigator decision (wild type *KIT*)

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

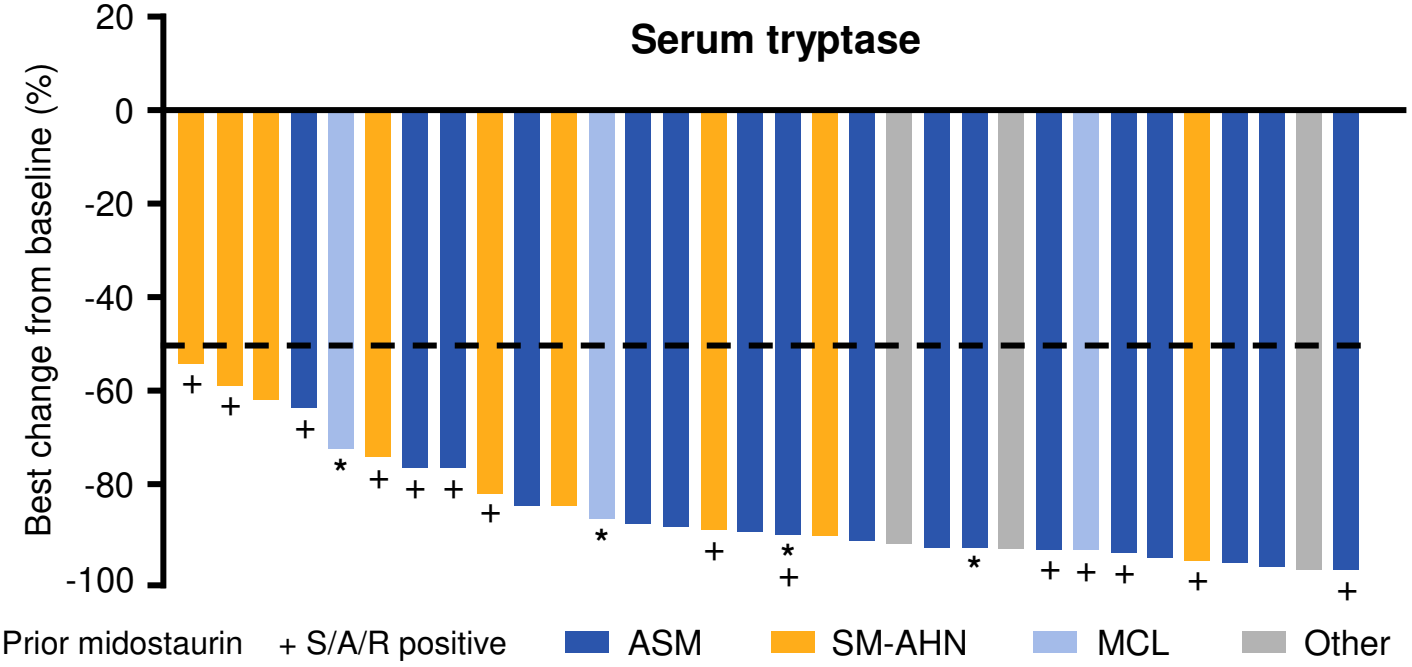
Data cut-off: 4 Oct 2017

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



MAF, mutant allele fraction

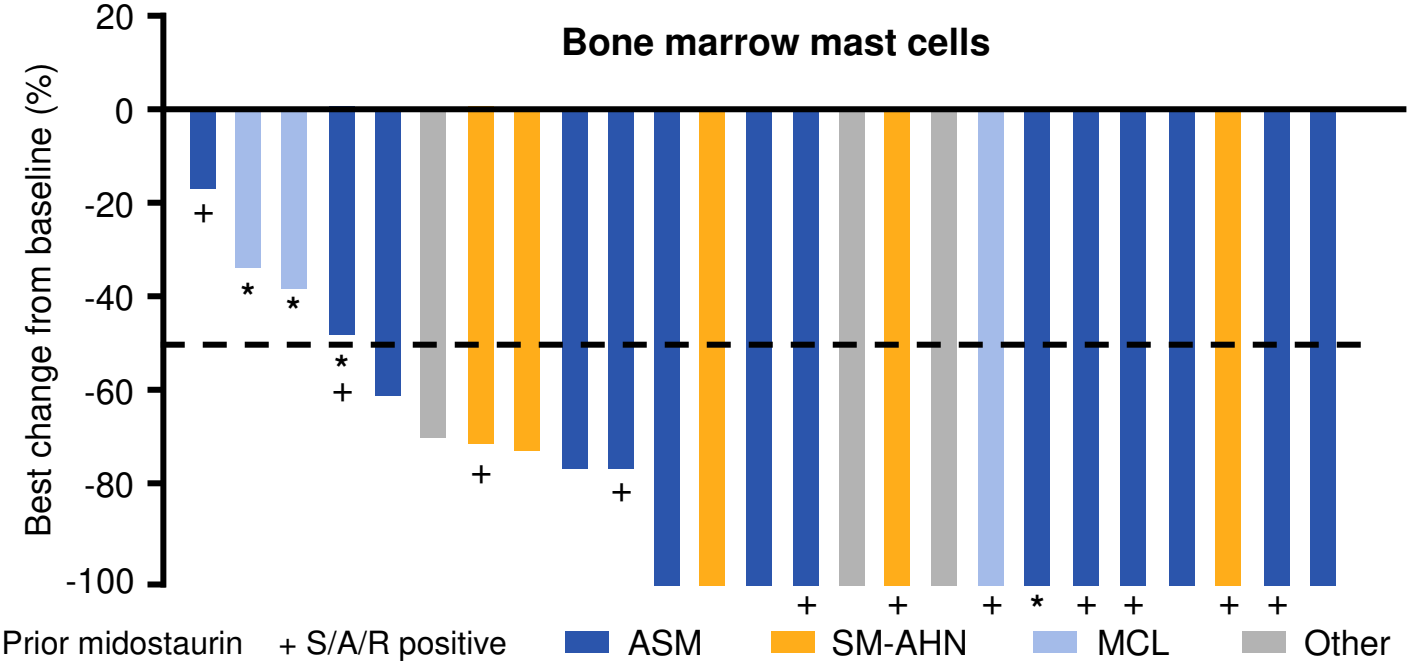
Tryptase decrease in all patients



- Baseline median 124 µg/L, range 14 to 1414 µg/L
- All 32 patients achieved >50% reduction from baseline

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

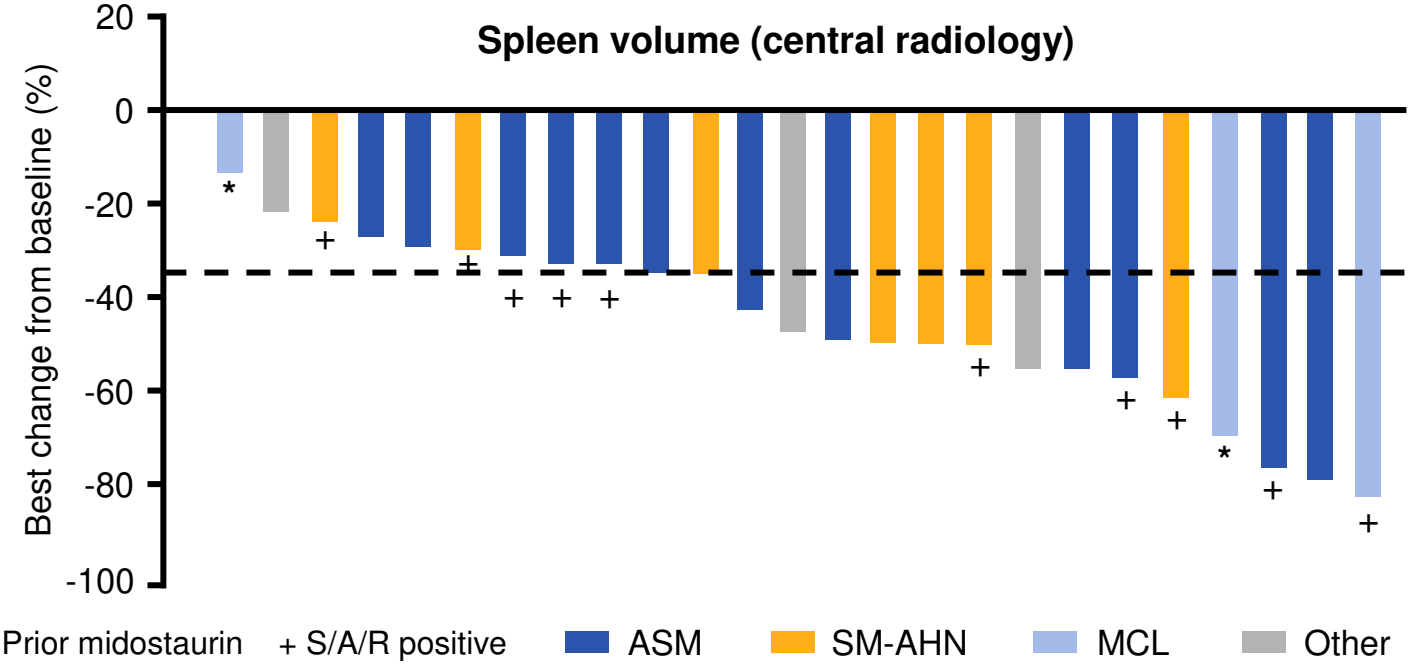
Bone marrow mast cell decrease in all patients^



- 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^

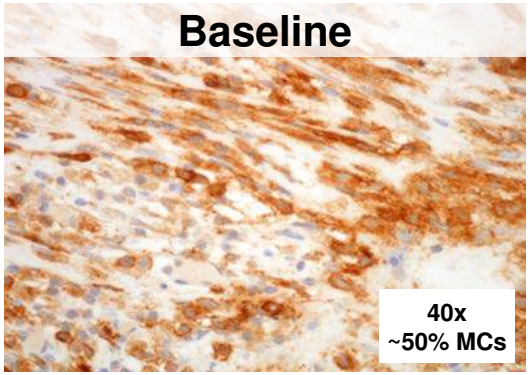


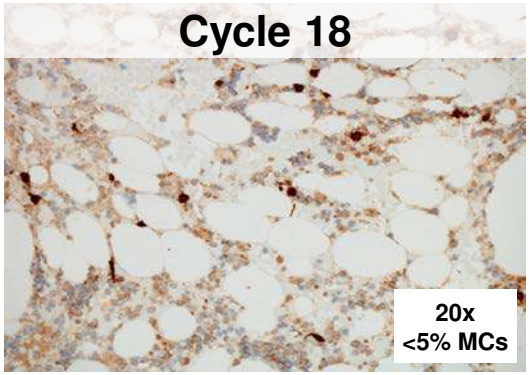
- Baseline median 633 mL, range 130 to 1952 mL
- ^n=25 patients with splenomegaly as per central assessment
- 15/25 (60%) patients achieved >35% reduction of spleen volume

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

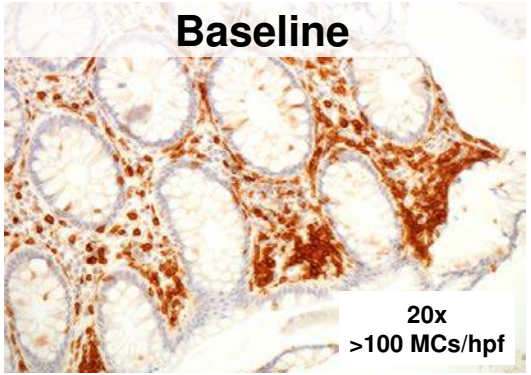
45-year-old female with ASM

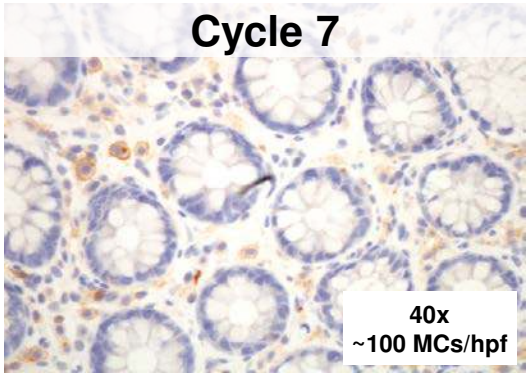
Bone marrow tryptase





Colon CD25



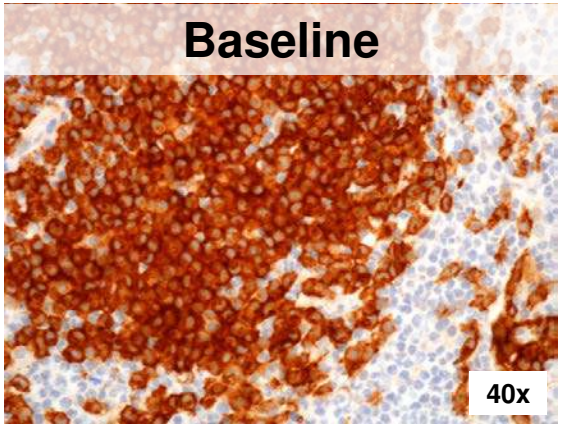


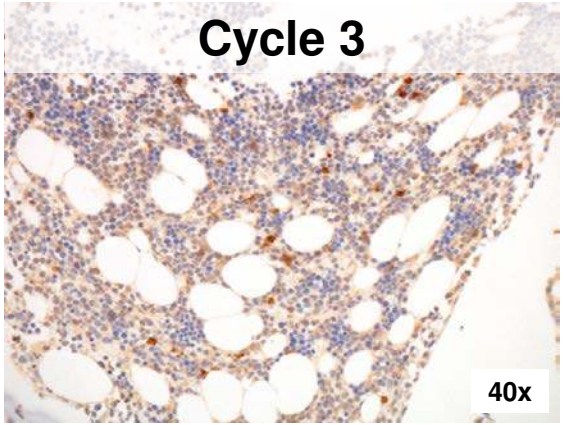
*BLU-285 60 mg; remains on treatment at cycle 18 with confirmed PR per IWG-MRT-ECNM

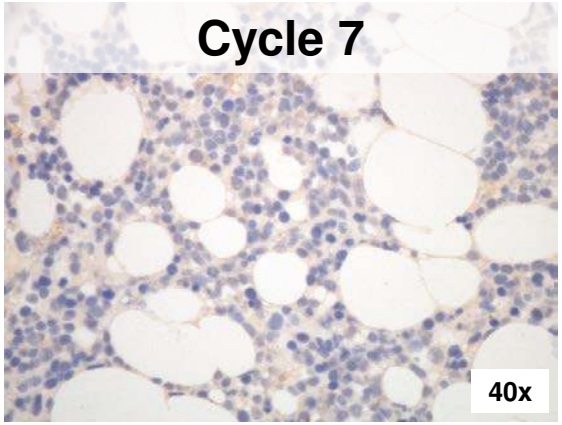
Images courtesy of Dr Deepti Radia, Guy's and St. Thomas NHS Trust

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

Images courtesy of Dr Deepti Radia, Guy's and St. Thomas NHS Trust

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]

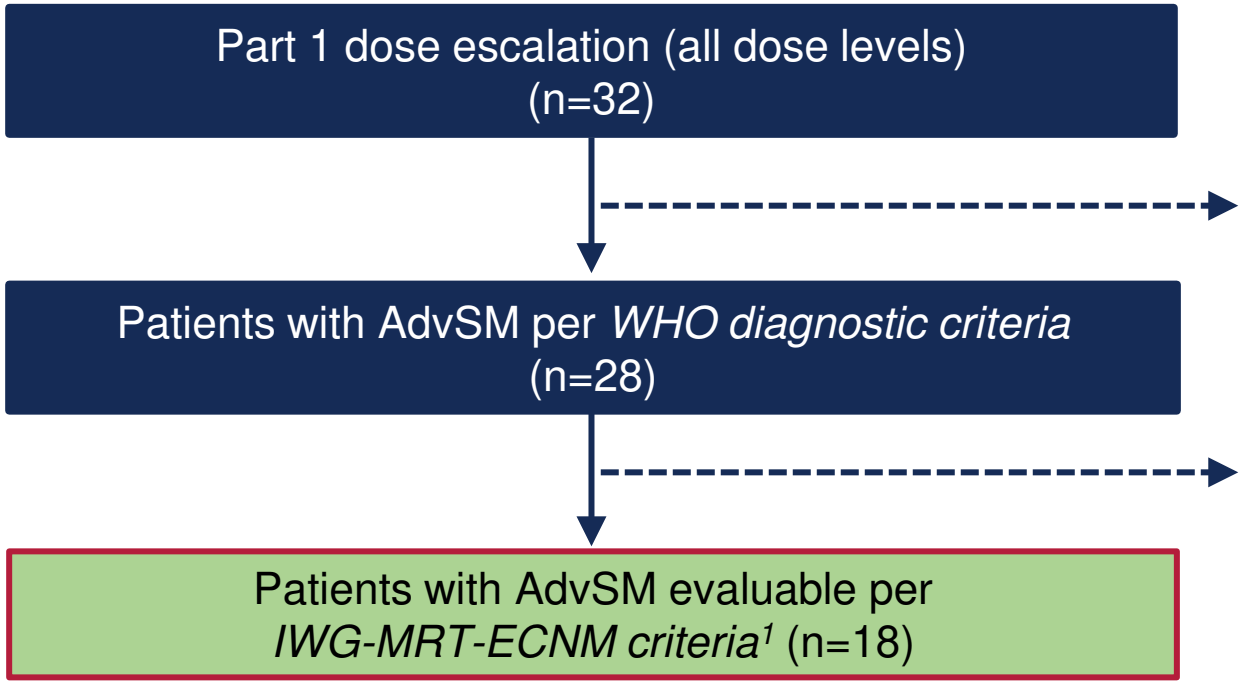
- ≥50% reduction in bone marrow mast cell aggregate
- ≥50% reduction in serum tryptase
- Resolution of 1 or more C-findings

Clinical improvement (CI)[1]

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

[1]Gotlib, et al. Blood. 2013 Mar 28; 121(13): 2393–2401

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 criteria[1]

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
  - Mark Drummond, Beatson West of Scotland Cancer Centre
  - Elizabeth Hexner, Abramson Cancer Center at the University of Pennsylvania
  - Albert Quiery, University of Michigan Comprehensive Cancer Center
  - Dan DeAngelo, Dana-Farber Cancer Institute
  - Michael Deininger, University of Utah, Huntsman Cancer Institute
  - Srdan Verstovsek, MD Anderson Cancer Center
  - William Robinson, University of Colorado
  - Jason Gotlib, Stanford Cancer Institute
- We thank Tracy George, Hans Peter Horny, and Maureen Conlan for expert technical analyses
- We also thank Sarah Jackson, PhD, of iMed Comms, an Ashfield company, who provided editorial writing support funded by Blueprint Medicines