Preliminary Safety and Activity in a Phase 1 study of BLU-285, a Potent, Highly-Selective Inhibitor of KIT D816V in Advanced Systemic Mastocytosis (SM)

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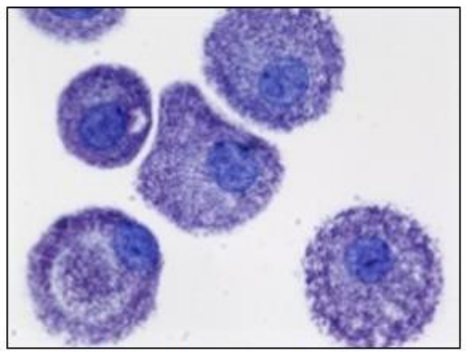
Advanced Systemic Mastocytosis

- **Mast cell neoplasm with poor prognosis and no effective treatments**
  - **Aggressive Systemic Mastocytosis (ASM); SM with associated hematologic neoplasm (SM-AHN); mast cell leukemia (MCL)**
- **KIT mutation D816V is a key driver in ~90-95% of patients[1]**

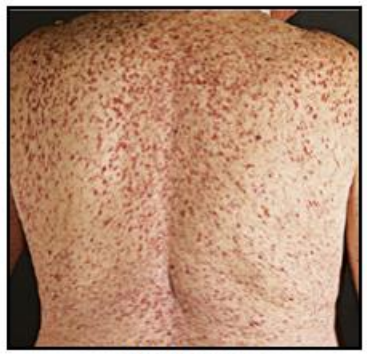
Mast cell accumulation and organ infiltration

Blood*



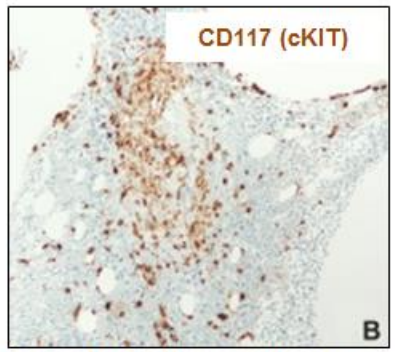
MC degranulation
MC mediator Sx
↑tryptase

Skin$



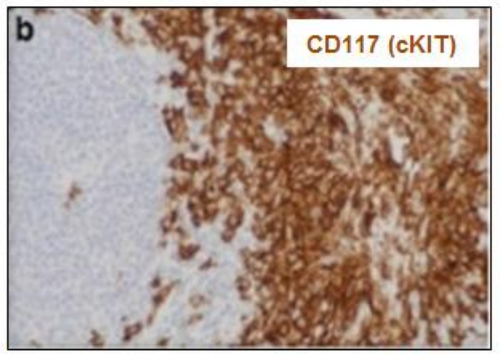
Urticaria pigmentosa

Bone and bone marrow*



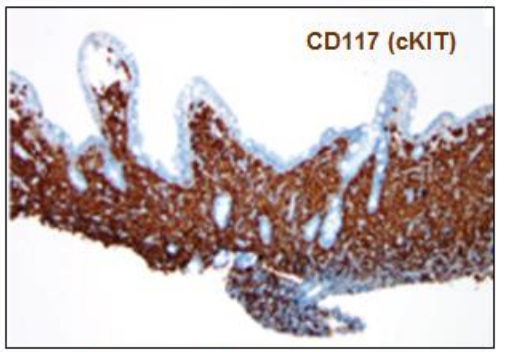
Osteolytic bone lesions
Cytopenias

Liver and spleen†



Liver function abnormalities,
Ascites, or Hypersplenism

GI tract‡



Hypoalbuminemia
Weight loss

C-findings

MC, mast cell; MCL, mast cell leukemia; SM, systemic mastocytosis; C- findings, clinical findings

[1]Garcia-Montero AC et al (2006)

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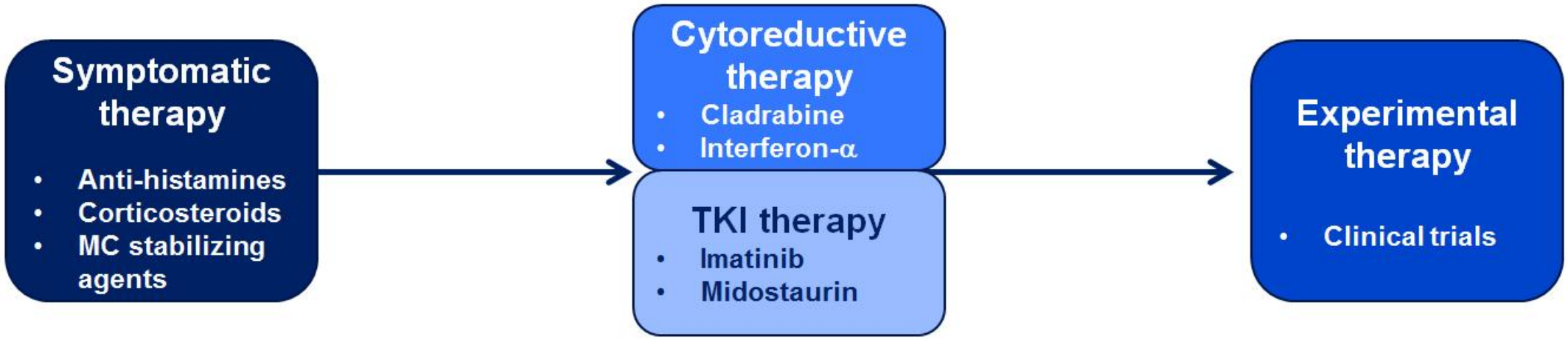
Advanced SM has High Medical Need

Current therapy does not eradicate KIT D816V



Advanced SM subtype	Life expectancy (months)
ASM	~41
SM-AHN	~24
MCL	~2

[1]Lim KH et al (2009)

- ↓Life expectancy with current therapy[1]
- Morbidity via C-findings
  - Cytopenias
  - Osteolytic bone lesions
  - Hepatomegaly with liver dysfunction
  - Hypersplenism
  - Malabsorption with weight loss

KIT, receptor tyrosine kinase protein; TKI, tyrosine-kinase inhibitor

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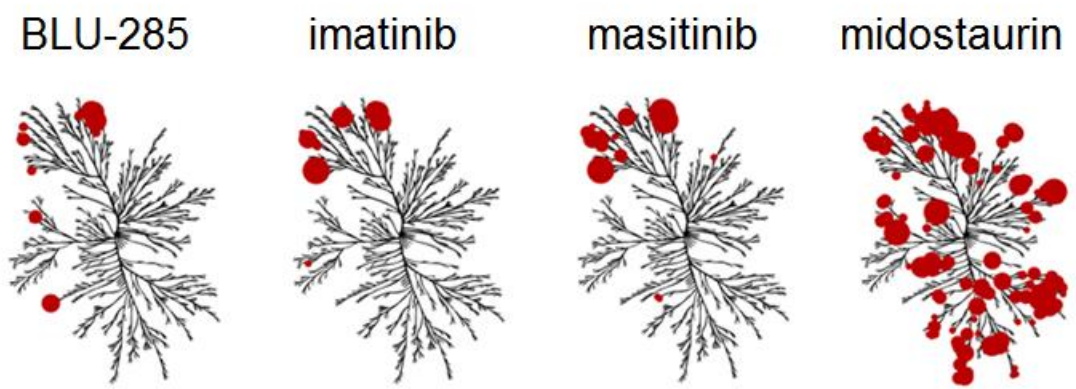
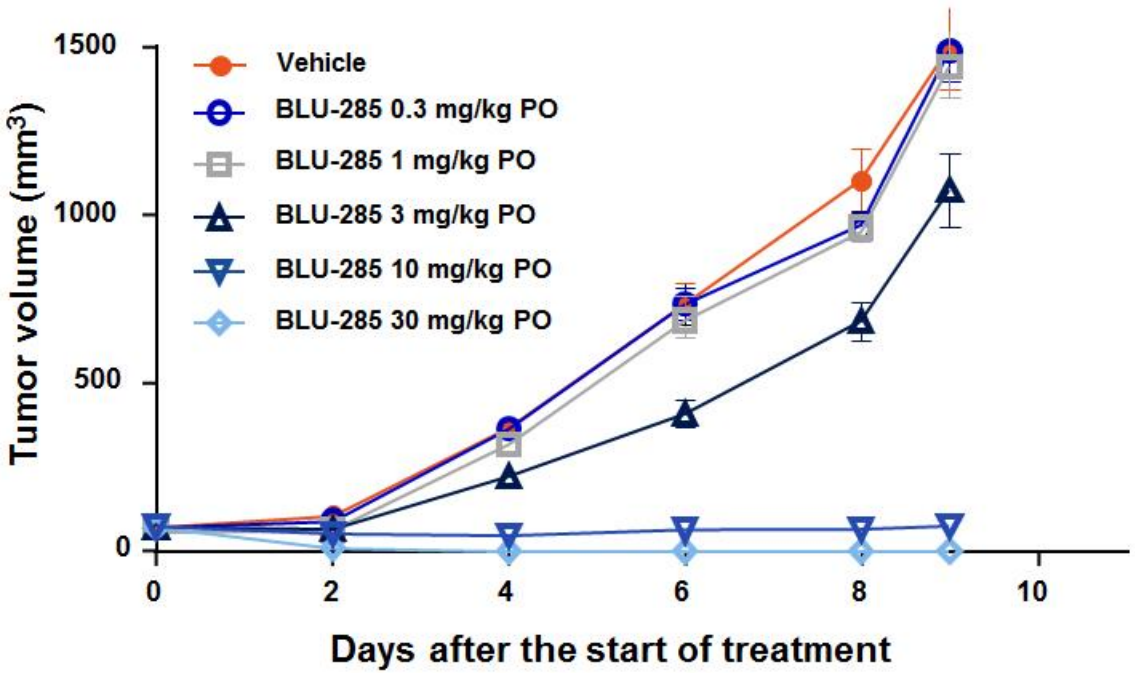
BLU-285: Potent, Highly Selective KIT D816V Inhibition

Biochemical profiles

	KIT D816V	
	IC_{50} (nM)	K_D (nM)
BLU-285	0.27	0.6
imatinib	8,150	> 10K
masitinib	> 10K	> 10K
midostaurin	2.8	3.4



Anti-tumor activity in KIT-driven mastocytoma model[1]



Model driven by KIT mutation equivalent to human KIT D816 mutation

IC_{50}, half maximal inhibitory concentration; K_D, dissociation constant; PO, orally

[1]Evans E et al (2014)

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

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Key Entry Criteria

- Any of the following diagnoses:
  - Aggressive Systemic Mastocytosis (ASM)[1]
  - SM with associated hematologic disorder (SM-AHN)[1] with ≥ 1 C-finding
  - Mast Cell Leukemia (MCL)[1]
  - Relapsed or refractory myeloid malignancy (dose escalation only)[2]
- Age ≥ 18
- ECOG performance status 0–3
- Platelet count ≥ 25 x 10^9 /L
- ANC ≥ 0.5 x 10^9 /L
- Adequate hepatic and renal function

ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group
[1]ASM, SM-AHNMD, or MCL per WHO criteria via local diagnosis and retrospective central pathology to confirm mastocytosis subtype. [2]Per IWG-MRT or WHO diagnostic criteria

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BLU-285 Phase 1 Objectives and Design

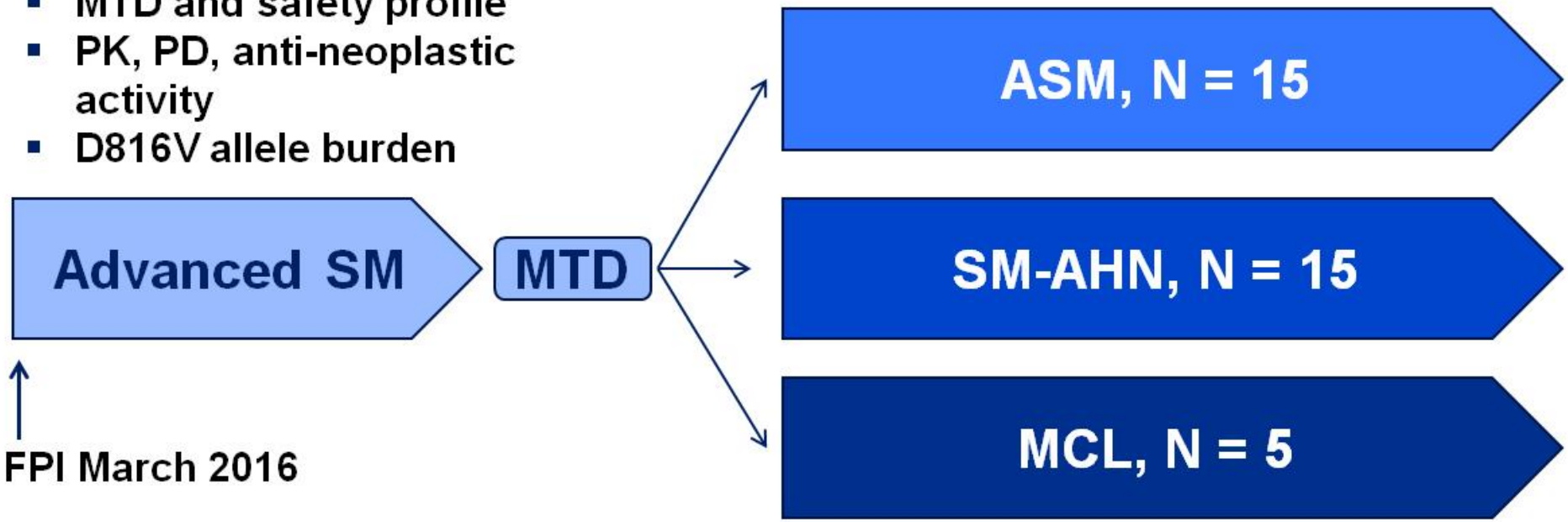
Enrolling

3 + 3 dose escalation

- MTD and safety profile
- PK, PD, anti-neoplastic activity
- D816V allele burden

Dose expansion

- Response rate per IWG-MRT-ECNM criteria[1]
- D816V allele burden
- Advanced SM- PRO



BLU-285 continuous once-daily oral dosing

FPI, first patient-in; IWG-MRT-ECNM, International working group – myeloproliferative neoplasms research and treatment – European; competence network on mastocytosis; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; SM-PRO, systemic mastocytosis patient reported outcomes

[1]Gotlib J et al (2013); NCT02561988

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Demography and Baseline Patient Characteristics

Parameter (all data are preliminary as of 11 November 2016 cutoff)	All patients, N = 12
Disease subtype per local assessment, n (%)	
ASM	8 (67)
MCL	1 (8)
SM-AHN (all AHN are CMML)	3 (25)
KIT D816V mutation, n (%)	11 (92)[1]
ECOG performance status, n (%)	
0	2 (17)
1	10 (83)
Prior anti-neoplastic therapy, n (%)	6 (50)[2]
Number of C-findings median (range)	1 (1–3)
Cytopenias, n (%)	6 (50)
Osteolytic bone lesions	2 (17)
Hepatomegaly with liver dysfunction	2 (17)
Hypersplenism	5 (42)
Malabsorption with weight loss	4 (33)
Uriticaria Pigmentosa / Other SM-related skin rash, n (%)	8 (67)

SM-CMML, systemic mastocytosis with chronic myelomonocytic leukemia; pt, patient
[1]One pt had no detectable KIT D816V mutation in blood or bone marrow; [2]2 pts had midostaurin;1pt had cladribine; 1 pt had Pegasys; 1 pt had interferon alpha-2; 1 pt had hydroxyurea and 5-azacitidine

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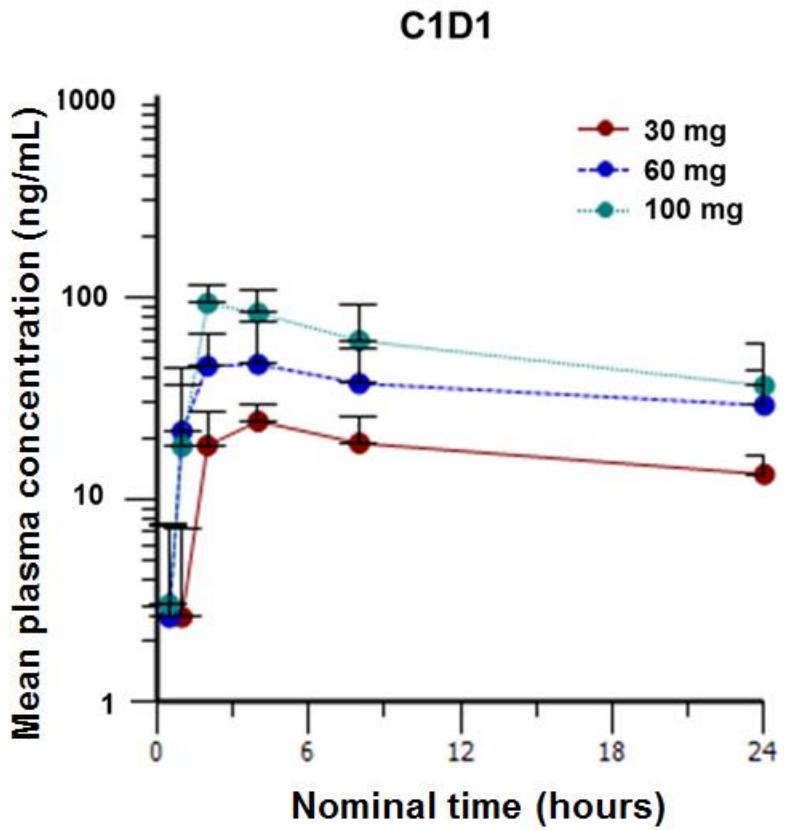
Initial Dose Escalation and PK Results

BLU-285 mg/day	Patients treated N = 12	DLT
30	3	0
60	6	1
100	3	0
130	Enrolling	



- Dose-dependent increase in exposure
- Rapid absorption: t_{max} 2–4 hours
- Half-life > 19 hours supports QD dosing

C1D1, cycle 1 day 1; DLT, dose limiting toxicity; t_{max}, time at which C_{max} is observed; QD, once daily

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Adverse Events

Non-hematological adverse events ≥ 2 patients (safety population, N = 12)		
Adverse event	Any grade n (%)	Grade 3 n (%)
Fatigue	4 (33)	0
↑ Alkaline Phosphatase	3 (25)	3 (25)
Diarrhea	2 (17)	0
Dizziness	2 (17)	0
Headache	2 (17)	0
Nausea	2 (17)	0
Pruritus	2 (17)	0

Hematological adverse events (safety population, N = 12)		
Adverse event	Any grade n (%)	Grade 3 n (%)
Anemia	3 (25)	0
Thrombocytopenia	2 (17)	1 (8)
Neutropenia	0	0

- Most AEs were CTCAE Grade 1 or 2
- No Grade 4 or 5 treatment-related events and no dose reductions required for toxicity
- 1 DLT : Grade 3 alkaline phosphatase elevation
- MTD has not been reached

AE, adverse event; CTCAE, common terminology criteria for adverse events; MTD, maximum tolerated dose

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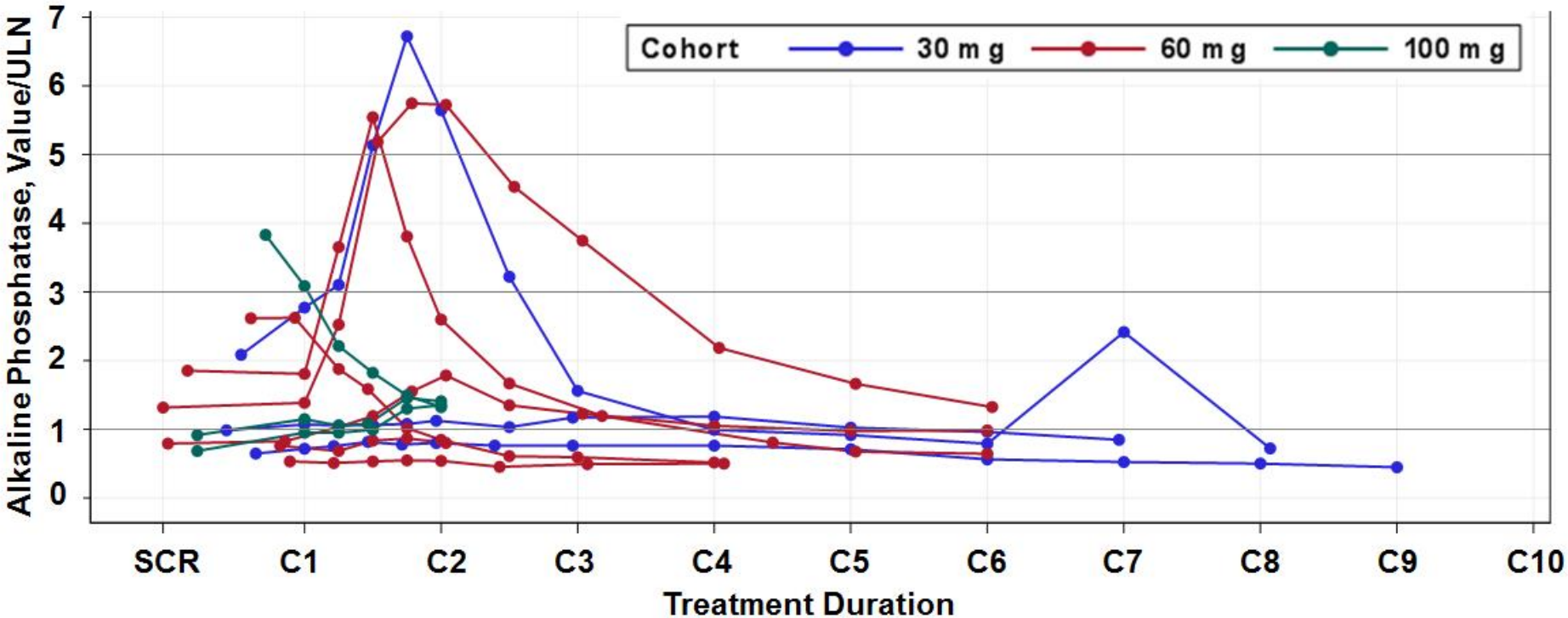
Alkaline Phosphatase Elevation is Likely a PD Effect on Bone Marrow Mast Cells



- Asymptomatic, transient Grade 3 alkaline phosphatase elevation occurred in the 3 patients with highest baseline bone marrow (BM) MC burden
- No associated transaminase or bilirubin elevation
- Confirmed bone origin in 1 patient (2 others not assessed)
- May represent a PD effect on BM MCs
- Protocol amended to consider only Grade 4 alkaline phosphatase elevation a DLT

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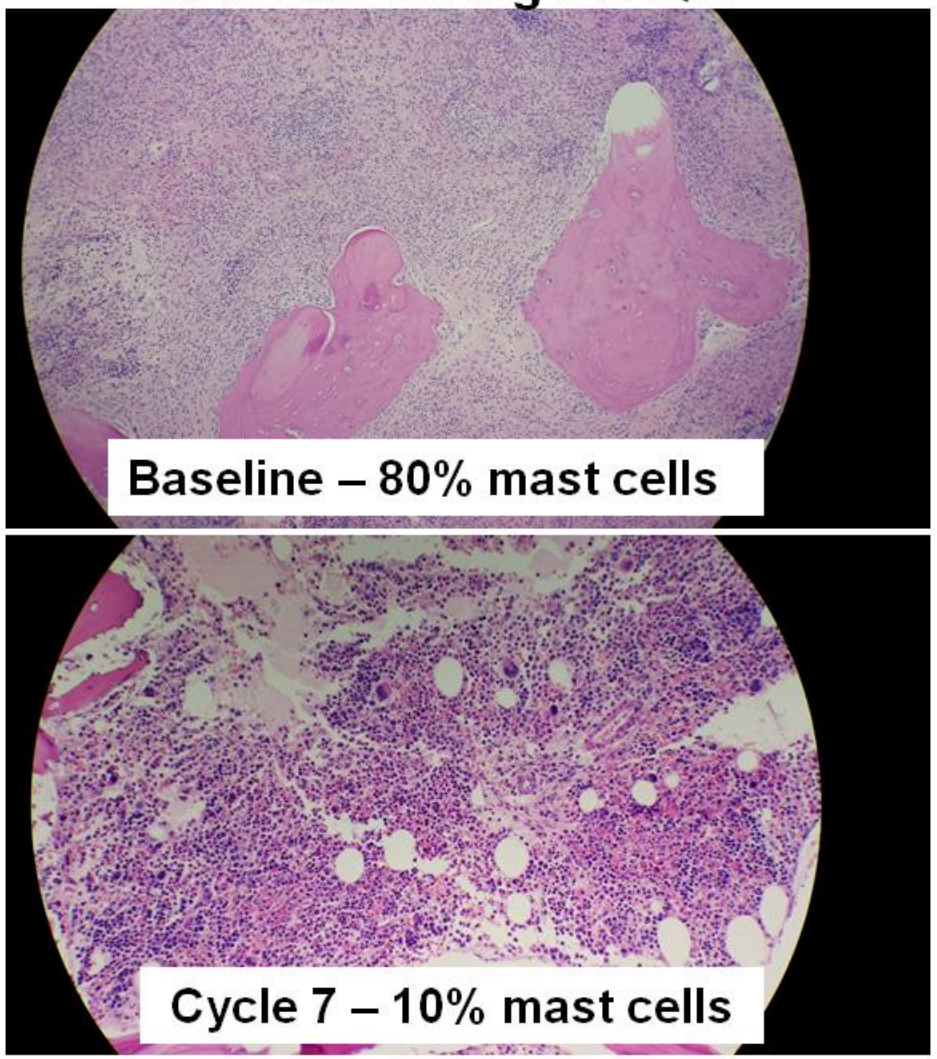
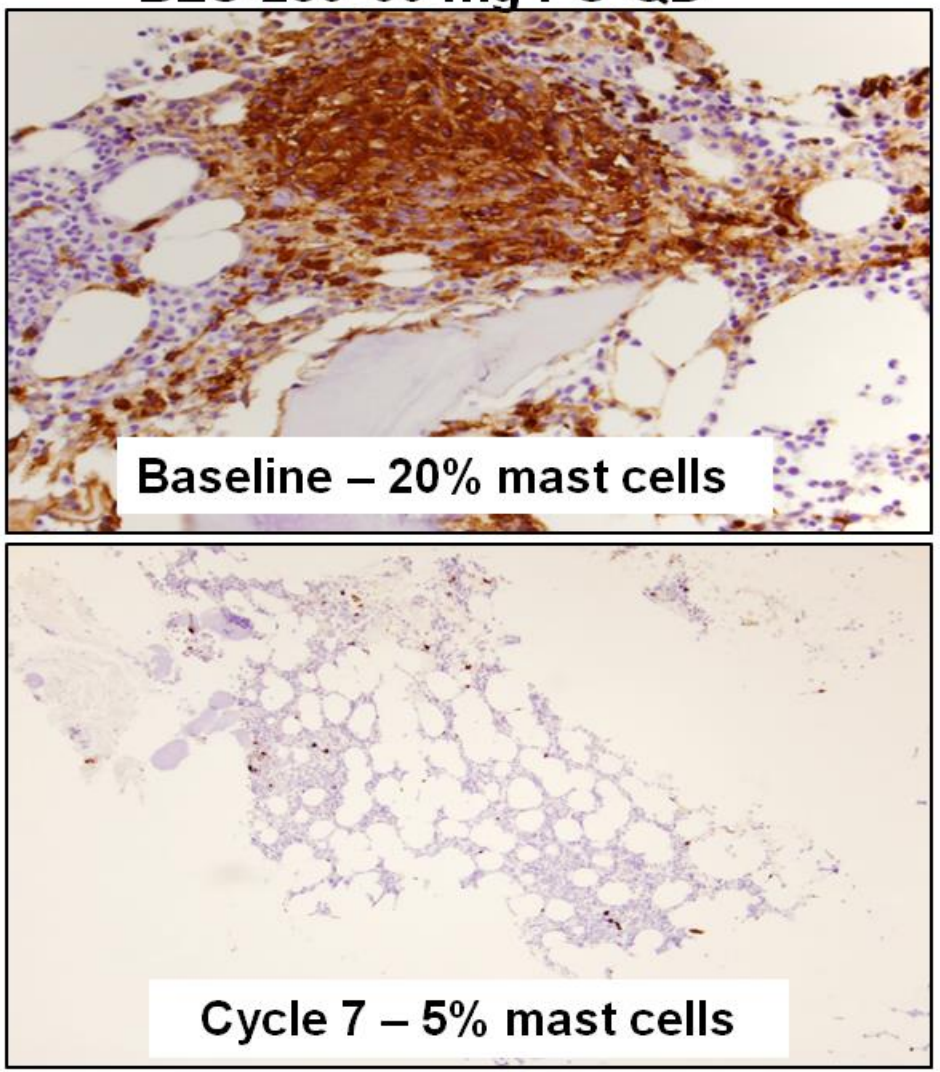
BLU-285 Markedly Reduces Bone Marrow Mast Cells

Aggressive Systemic Mastocytosis
BLU-285 30 mg PO QD



Aggressive Systemic Mastocytosis
BLU-285 60 mg PO QD*



*Dr. Mohamed E. Salama, Hematopathology Huntsman Cancer Institute University of Utah

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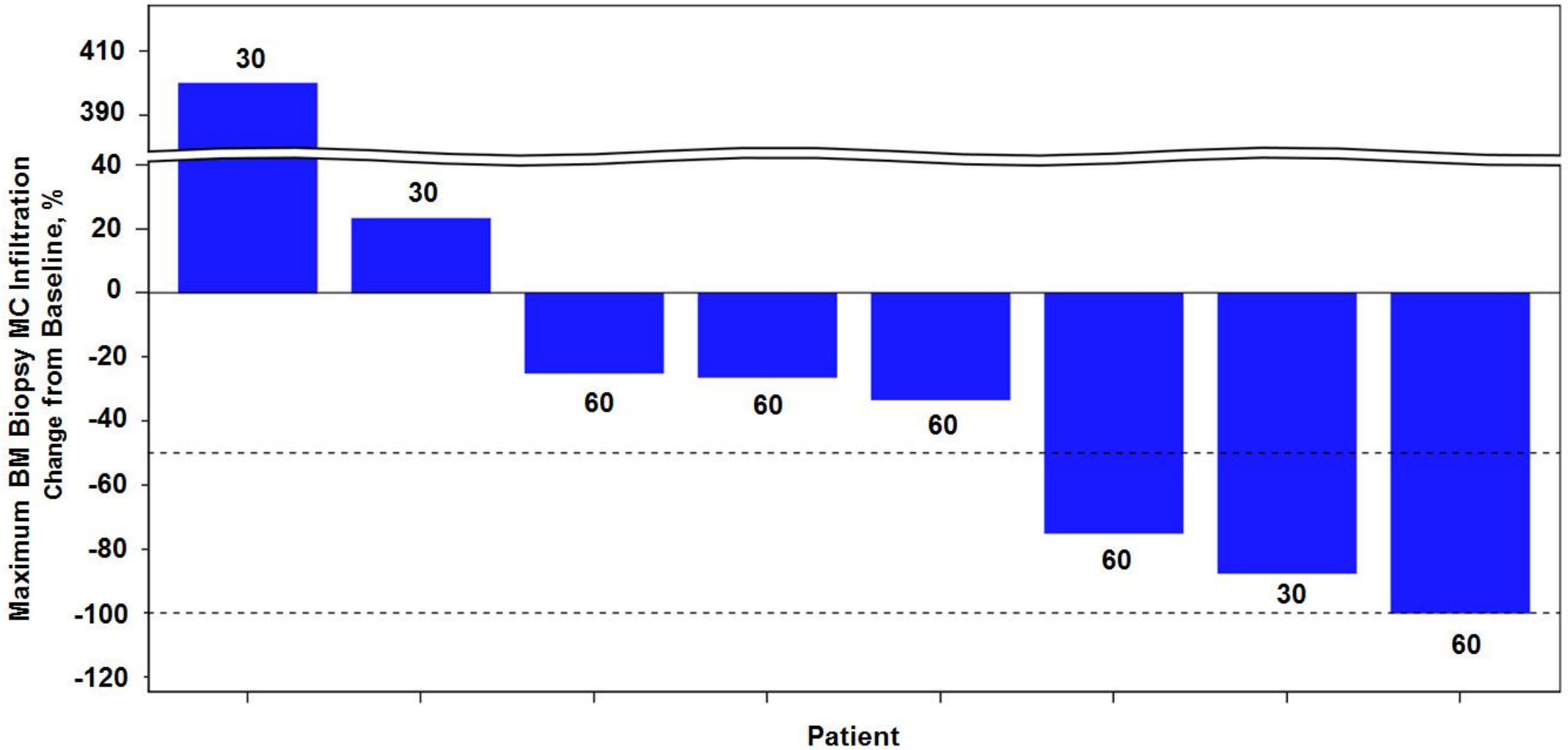
Decreased BM Mast Cells in 6 of 8 Patients



BM, bone marrow
NB: The values above/below the bars denote the dose level (mg) QD received by each patient

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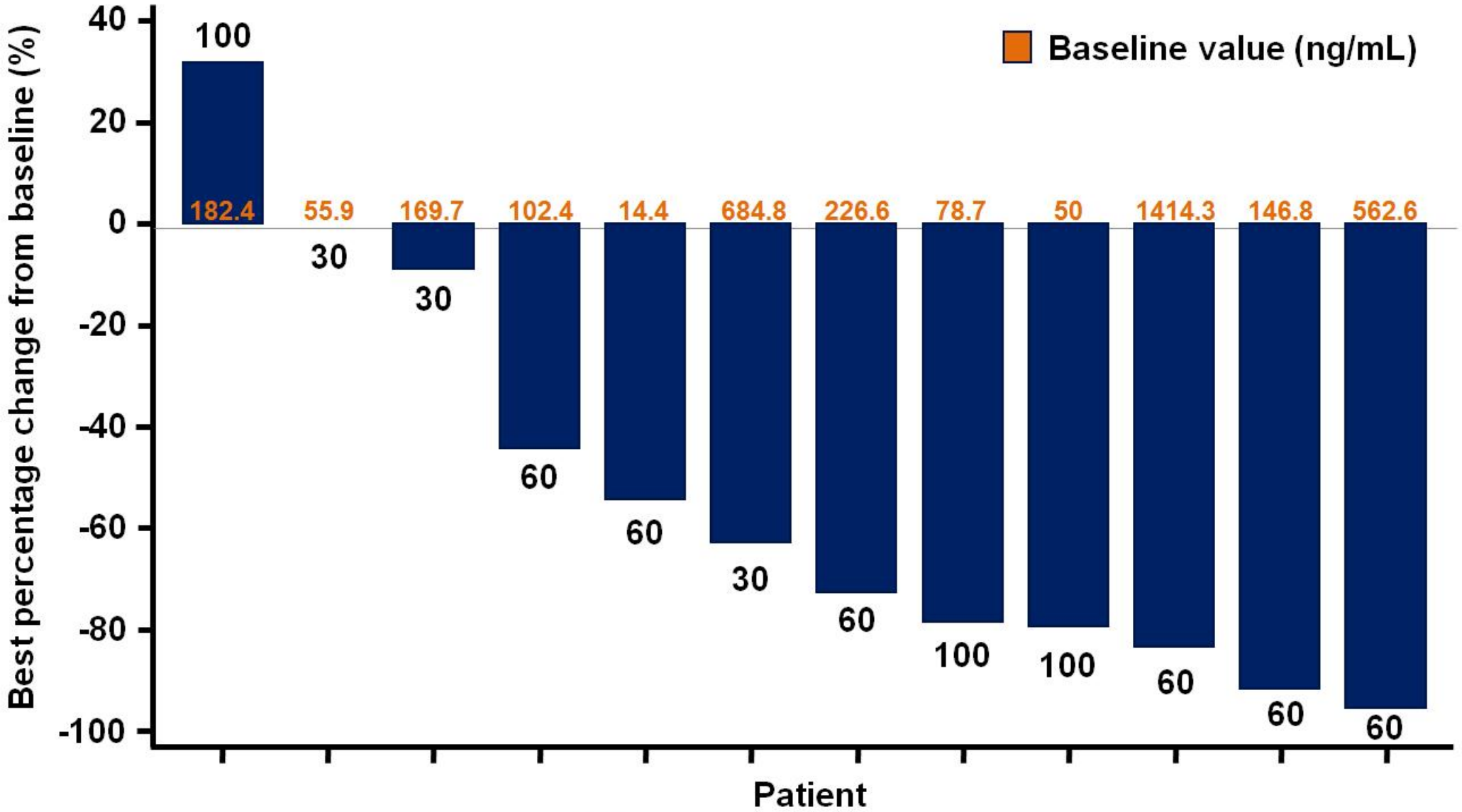
Decreased Tryptase in 10 of 12 Patients



NB: The values above/below the bars denote the dose level (mg) QD received by each patient

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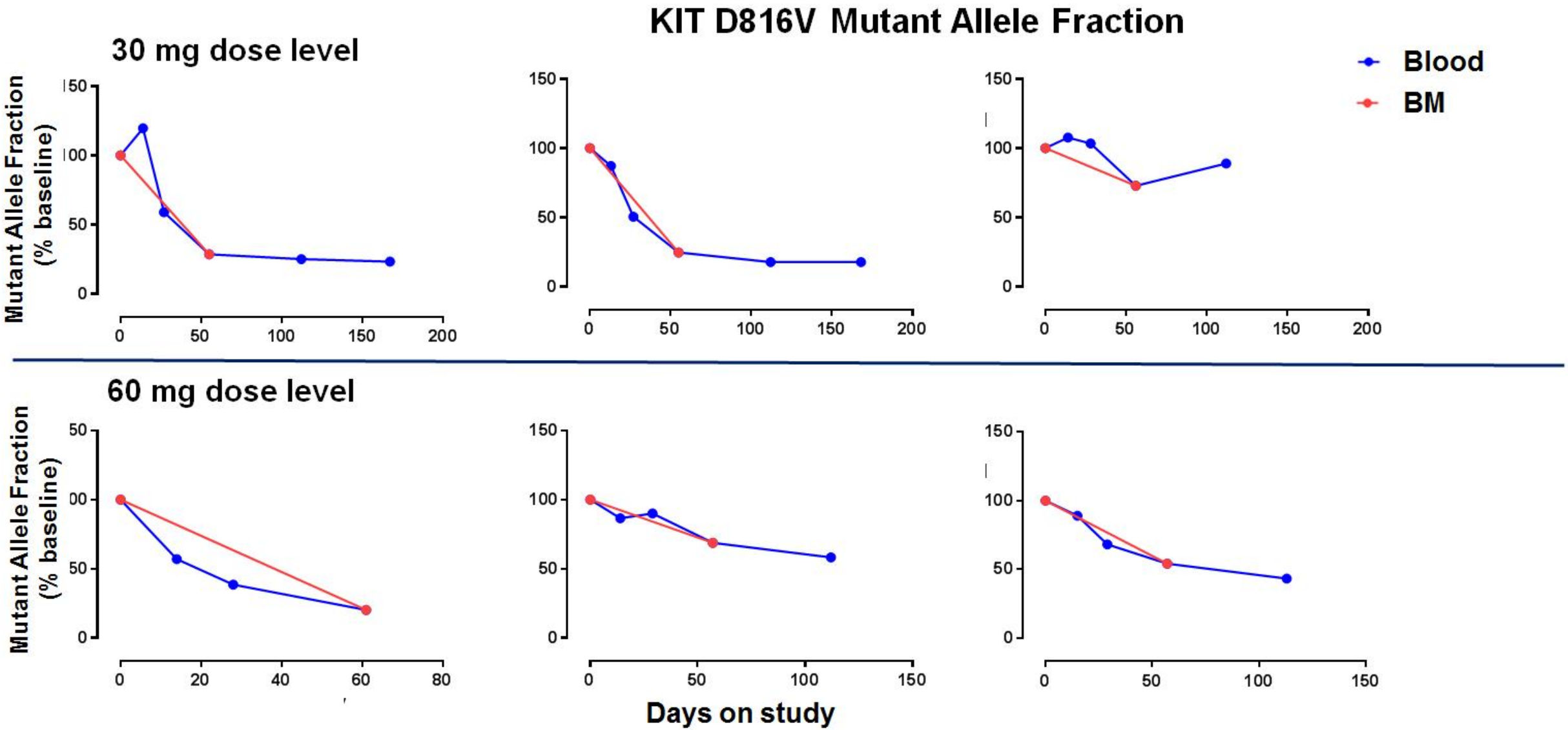
Molecular Response in Blood and BM



All available data as of data cutoff date shown

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Decreased Malabsorption and Rash

- Maximum weight gain from baseline (n =12):
  - Increase median 4.3 kg, range -0.5 – 12.9 kg
  - % increase median 4.7%, range -0.5 – 19.2%
- Maximum albumin gain from baseline (n = 12):
  - Increase median 0.45 g/dL, range 0 – 1.4 g/dL
  - % increase median 10.7%, range 0 – 40.0%
- Rash improved per investigator assessment in all 5 patients with Uriticaria Pigmentosa for whom data are available

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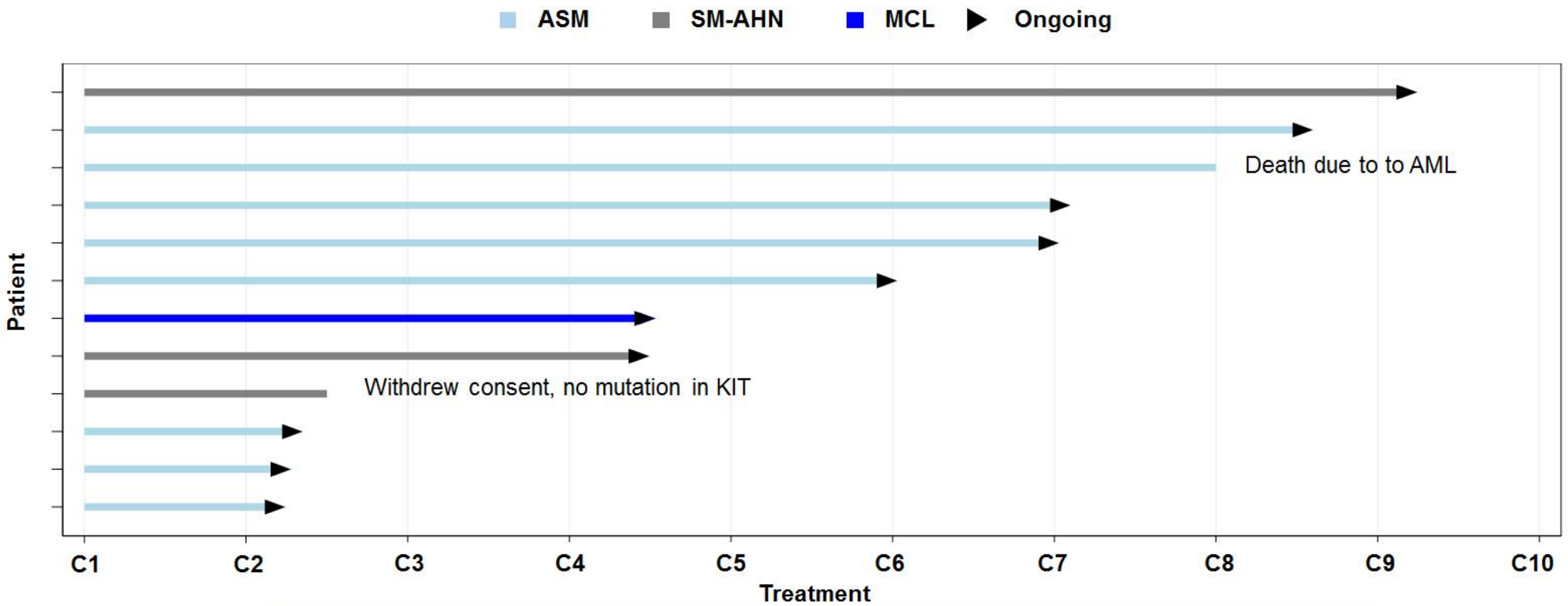
BLU-285 Duration on Study



10 (83%) patients remain on study, range 1 – 8.1 months

ASM, aggressive systemic mastocytosis; MCL, mast-cell leukemia; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm

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Summary

- BLU-285 has demonstrated encouraging clinical activity in advanced SM with marked decreases in mast cell burden and improved patient symptoms
- Data support the hypothesis that KIT D816V is a key disease driver in SM
- Half-life > 19 hours supports QD dosing
- BLU-285 has been well tolerated over a dose range of 30 to 100 mg - dose escalation (currently at 130 mg QD)
- BLU-285 deserves continued investigation in advanced SM, and further investigation in other KIT-driven diseases; Phase 1 study of BLU-285 in GIST is ongoing

GIST, gastrointestinal stromal tumor

Study sponsored by Blueprint Medicines Corporation

Acknowledgments

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  - Guy's & St Thomas NHS Trust
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  - Abramson Cancer Center at the University of Pennsylvania
  - University of Michigan Comprehensive Cancer Center
  - Dana-Farber Cancer Institute
  - University of Utah, Huntsman Cancer Institute
  - MD Anderson Cancer Center
  - University of Colorado
  - Stanford University

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  - Skin

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  - Liver and spleen

Annals of Hematology, Isolated splenomegaly as the only presentation of systemic mastocytosis, 92, 2013, pg. 1574 Figure 1, Nischala Ammannagari, Sara Grethlein, James J. Longhi, and John M. Fisk, Copyright Springer-Verlag Berlin Heidelberg 2013, With permission from Springer

  - GI tract

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