

BLU-285, A Potent and Selective Inhibitor for Hematologic Malignancies with KIT Exon 17 Mutations

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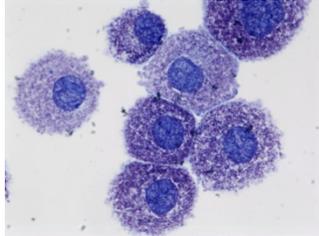
NHS Foundation Trust

London, UK

Disclosures

- BLU-285 is an investigational agent currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
- Deepti Radia is an investigator for Blueprint Medicine's ongoing phase 1 study in patients with advanced systemic mastocytosis
- Deepti Radia has received educational grants from Novartis and Pfizer

KIT Exon 17 Mutations Drive Several Diseases



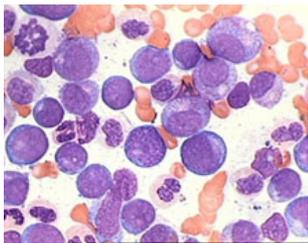
Systemic Mastocytosis

- ~ 95% KIT D816V
- MC organ infiltration causes significant organ damage in AdvSM



GIST

- > 80% KIT mutant
- Initially Imatinib responsive, but 2° Exon 17 mutation drives progression



AML

- ~15% CBF-AML KIT Exon 17 mutant
- KIT Exon 17 mutation ↑relapse and ↓survival

BLU-285: designed for potent, selective KIT D816V inhibition

	KIT D816V Potency		Kinome Selectivity
	IC ₅₀ (nM)	Binding (nM)	# kinases inhibited at 3 μM
BLU-285	0.27	0.6	13
Imatinib	8,150	>10K	13
Masitinib	>10K*	>10K	13
Dasatinib	1.6	1.7	90
Midostaurin	2.8	3.4	119

BLU-285 *In vitro* Profile

- ~ 6 to > 30,000-fold more potent
- ~ 7 to 10-fold more selective

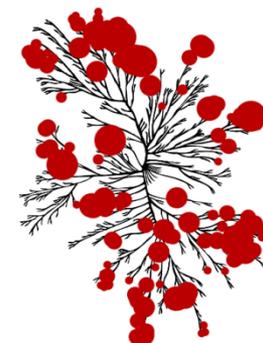
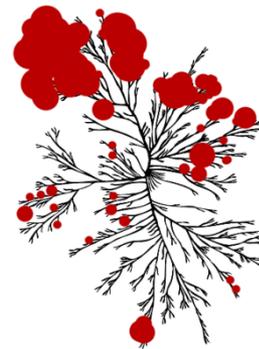
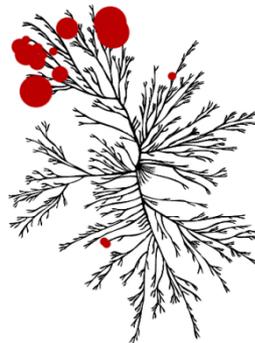
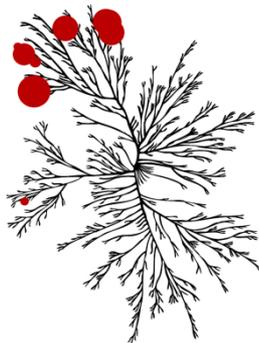
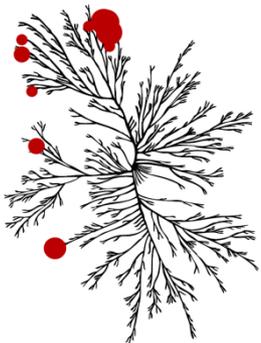
BLU-285

Imatinib

Masitinib

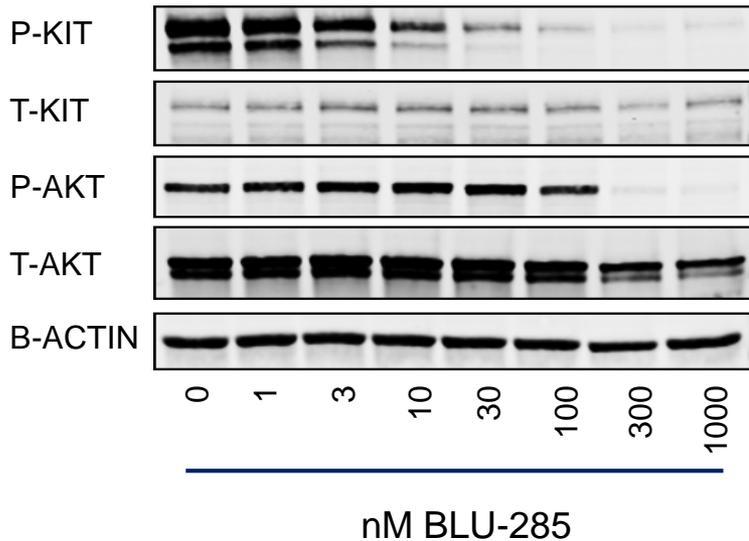
Dasatinib

Midostaurin



BLU-285 has potent *in vitro* activity against disease-driving KIT Exon 17 Mutants

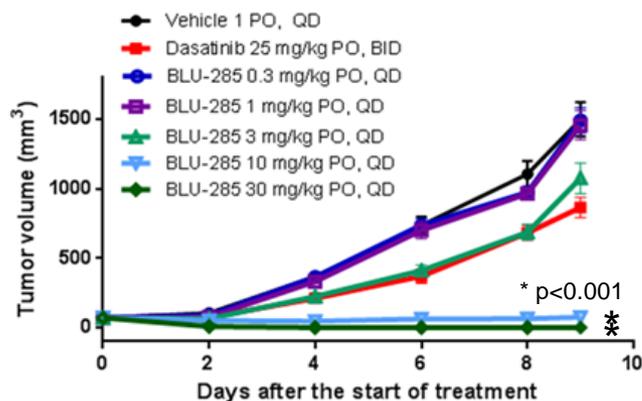
Mast Cell Leukemia (HMC1.2) KIT Inhibition



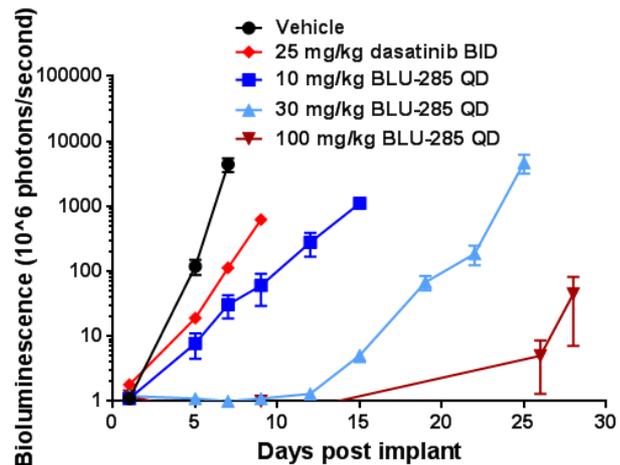
Indication (cell line)	KIT Mutation	KIT IC ₅₀ (nM)	Proliferation IC ₅₀ (nM)
Mast Cell Leukemia (MHC1.2)	Exon 11/17 (V560G/D816V)	4	125
Mastocytoma (P815)	Exon 17 (D816Y)	22	202
AML (Kasumi)	Exon 17 (N822K)	35	75
AML (M-07e)	None (dependent on WT KIT)	192	363
Prostate/pro-B/AML (non-KIT driven lines)	None (KIT - independent)	Not done	> 10,000

BLU-285 Induces Regression in KIT Exon 17 Mutant Mastocytosis Models

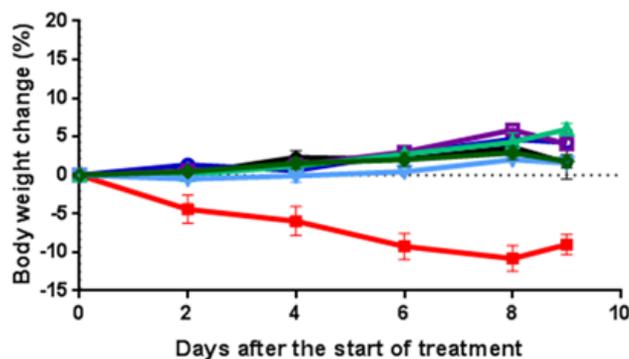
P815 Mastocytoma Model



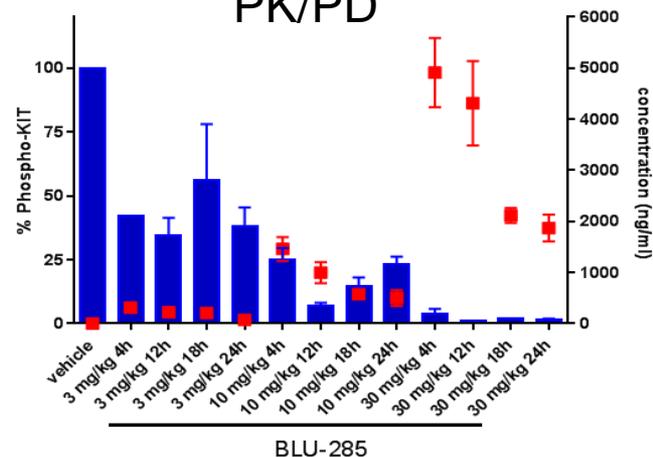
P815 Disseminated Mastocytosis Model



Tolerability – Body Weight



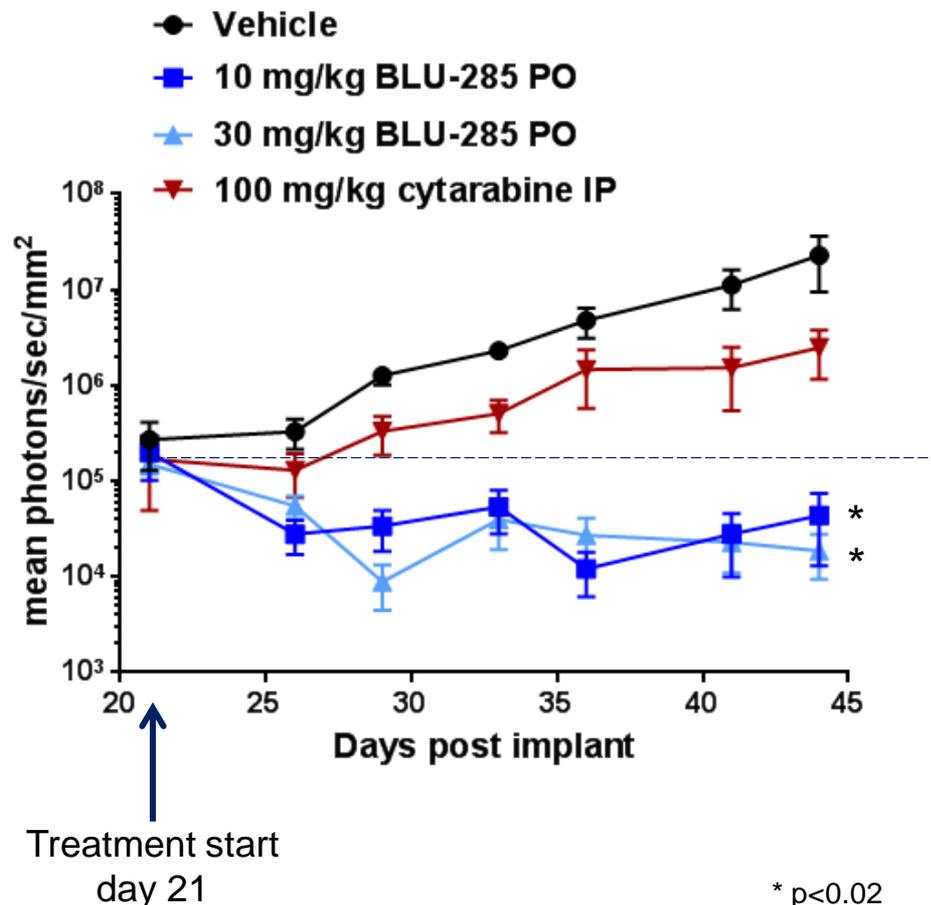
PK/PD



BLU-285 Induces Regression in the Kasumi-luc+ AML Model

Kasumi-luc+ AML model

- Kasumi cells engineered to stably express luciferase are injected intra-femorally into NOG mice
- After 21 day latency period, disease detected by whole body imaging
- Widespread disease in femurs, spleen, and vertebrae, detected by day 44
- BLU-285 active and well tolerated at 10 and 30 mg/kg once daily, oral dosing



BLU-285 Has Entered Two Phase 1 Clinical Trials in KIT Exon 17-driven disease

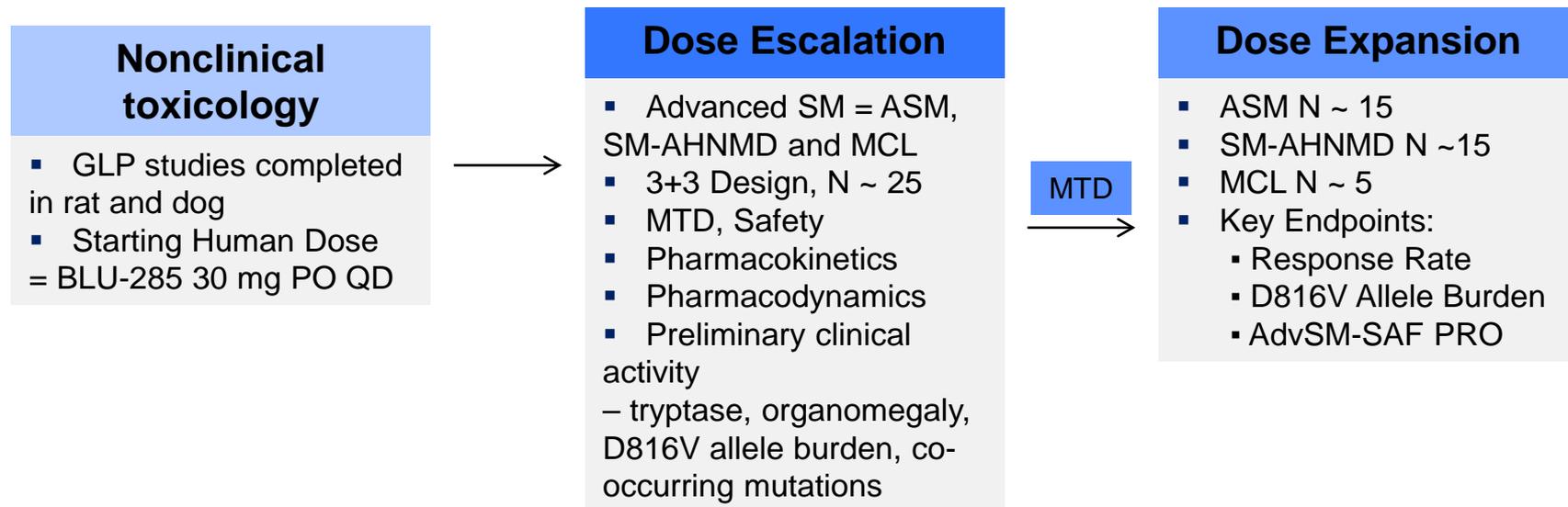
- Phase 1 Study of BLU-285 in Patients With Gastrointestinal Stromal Tumors (GIST) and Other Relapsed and Refractory Solid Tumors
 - ClinicalTrials.gov identifier NCT02508532
 - Initiated Q4 2015

- A Phase 1 Study of BLU-285 in Patients With Advanced Systemic Mastocytosis (advSM) and Relapsed or Refractory Myeloid Malignancies
 - ClinicalTrials.gov identifier NCT02561988
 - Initiated March 2016

BLU-285 Phase 1 Study in Advanced SM

	Objectives
Primary	<ul style="list-style-type: none">▪ Define MTD, RP2D, safety/tolerability
Secondary	<ul style="list-style-type: none">▪ Assess pharmacokinetics and pharmacodynamics▪ Assess D816V allele burden in blood and BM▪ Assess changes in patient reported outcomes▪ Define response rate and duration of response
Exploratory	<ul style="list-style-type: none">▪ Additional measures of antitumor activity (spleen volume, PFS, OS)▪ Correlate changes in KIT D816V allele burden with antitumor activity▪ Identify potential new blood and tumor biomarkers

BLU-285-2101 Study Design and Enrollment Status*



- 9 Sites (7 US, 2EU)
- First patient enrolled March 2016; Phase 1 study enrolling well, N = 12
- 30, 60, 100 mg dose levels enrolled

Conclusions

- BLU-285 is an oral, highly-selective, potent inhibitor designed to target KIT D816V and other KIT Exon 17 activation loop mutants
- BLU-285 shows potent in vitro and in vivo activity against KIT Exon 17 mutant mastocytosis and AML models
- A phase 1 study being conducted by Blueprint Medicines for BLU-285 in Advanced SM is ongoing
 - Abstract submitted to ASH meeting (December)
 - Additional Advanced SM clinical activities include
 - Mast Cell Connect patient registry with Patient Crossroads
 - Development of an Advanced SM patient reported outcome (PRO) measure
- BLU-285 has potential for further investigation for treatment of ISM and AML

Acknowledgements

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