

**BLU-285: A potent and highly selective inhibitor
designed to target malignancies driven by KIT and
PDGFR α mutations**

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New Drugs on the Horizon
2017 AACR Annual Meeting

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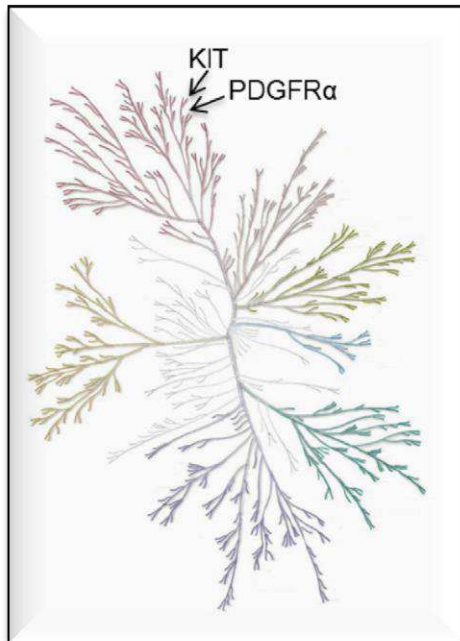
Disclosures

- Employee and shareholder of Blueprint Medicines
- BLU-285 is an investigational agent currently in development by Blueprint Medicines

Activating mutations in KIT and PDGFR α are disease drivers

KIT and PDGFR α

- Highly-related class III receptor tyrosine kinases
- Kinase activity normally requires ligand-induced dimerization
- PDGFR α activity: organogenesis, angiogenesis, vascular integrity
- KIT activity: hematopoiesis, melanocytes, germ cells



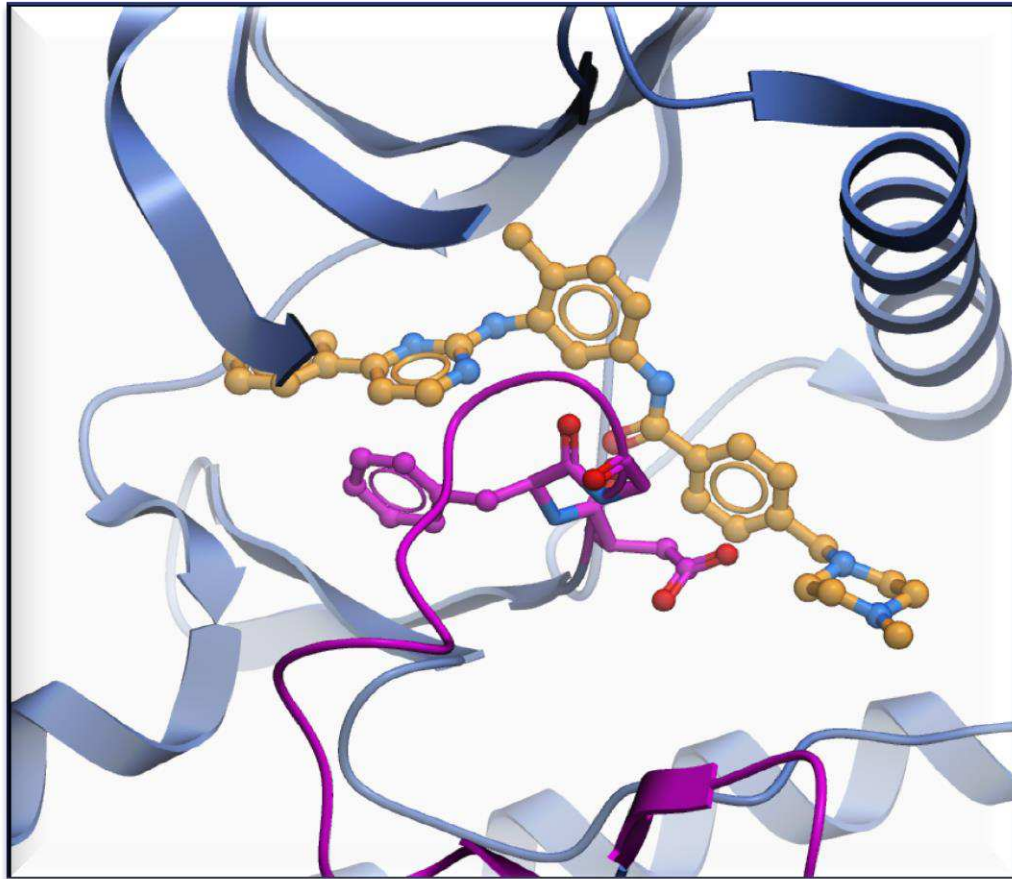
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

Mutation	Disease
PDGFR α Fusion	MDS, MPN, Eosinophilic leukemia
PDGFR α Exon 12	GIST
PDGFR α Exon 18	GIST
KIT Exon 9	GIST
KIT Exon 11	GIST, Melanoma
KIT Exon 13	GIST, Melanoma
	imatinib-resistant GIST
KIT Exon 17	Systemic Mastocytosis
	Acute Myeloid Leukemia
	Germ Cell Tumors
	imatinib/sunitinib-resistant GIST

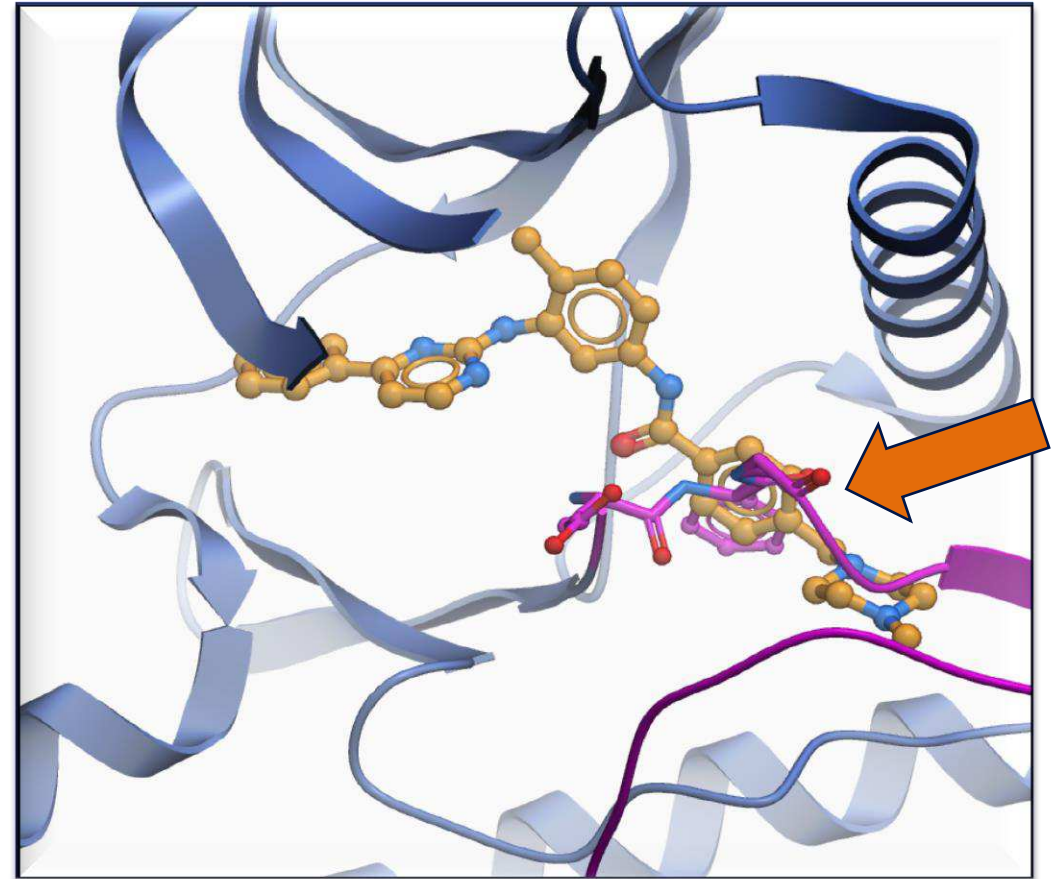
■ imatinib-sensitive

KIT activation loop mutations abrogate type II inhibitor binding

Imatinib binds inactive conformation of KIT/PDGFR α



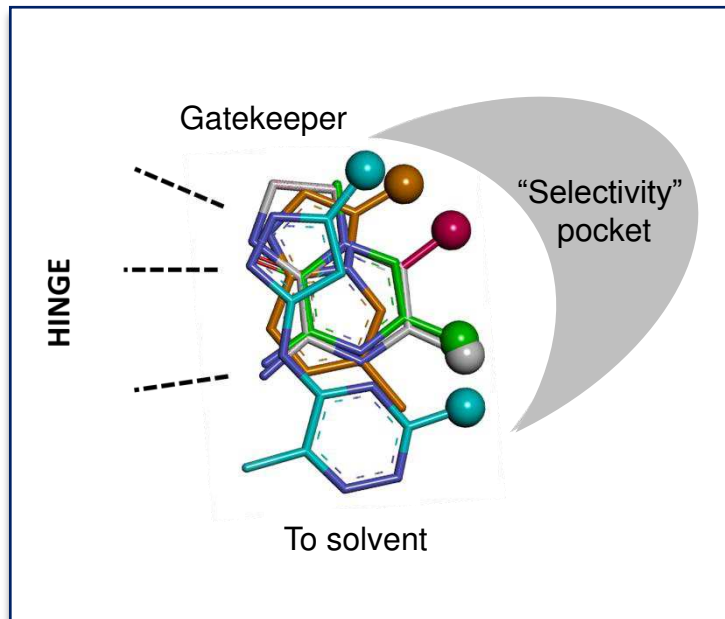
Inactive conformation
Activation loop closed, DFG-out
Type II inhibitors active



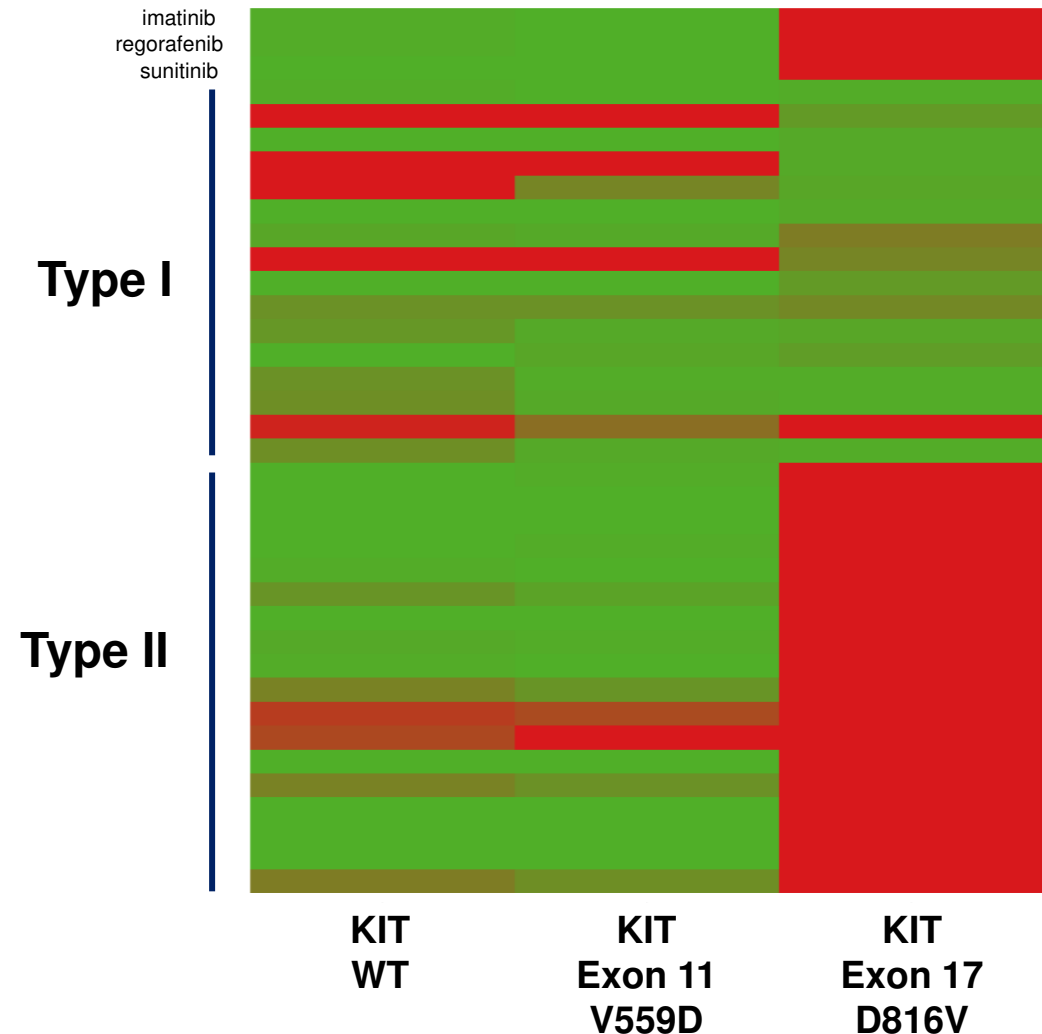
Active conformation
Activation loop open, DFG-in
Type II inhibitors inactive

Annotated library highlights type 1 inhibitor activity on KIT exon 17 and exon 11 activating mutations

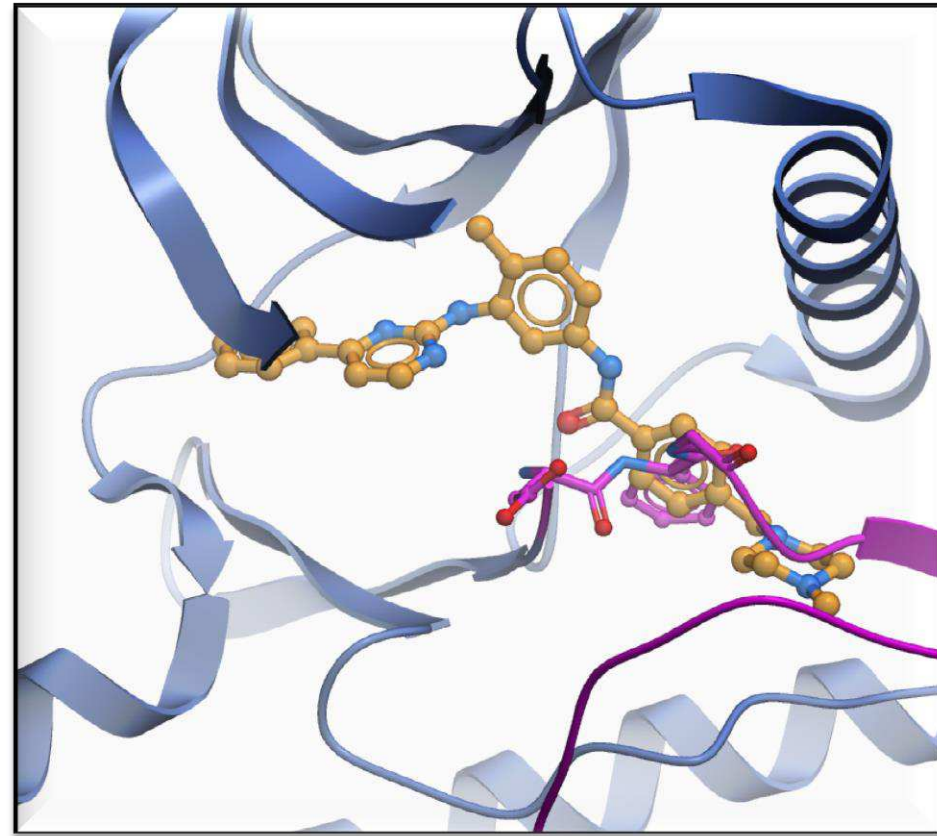
UNIQUE KINASE-DIRECTED COMPOUND LIBRARY



- Designed to balance novelty, potency, selectivity
- Broad and deep kinome coverage
- High quality, differentiated medicinal chemistry starting points fully annotated across human kinome



BLU-285 is a potent type 1 KIT/PDGFR α inhibitor that binds to the active conformation of the kinase



Imatinib
Activation loop open

*[chemical structure
for BLU-285 removed]*

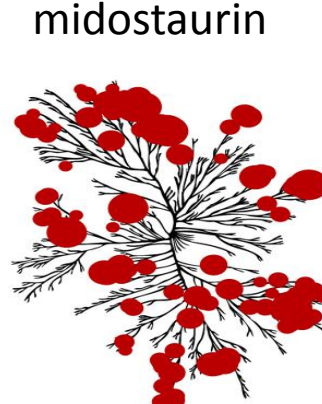
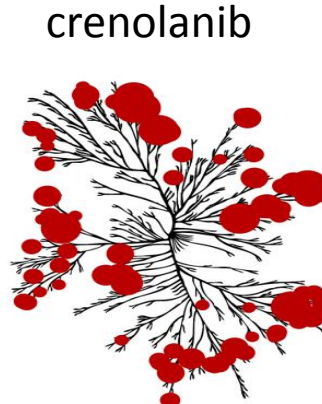
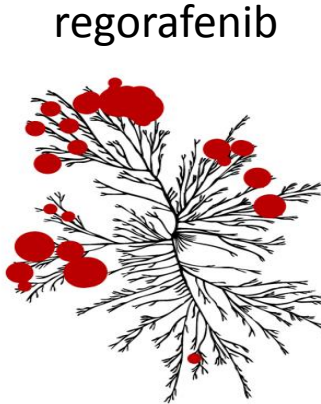
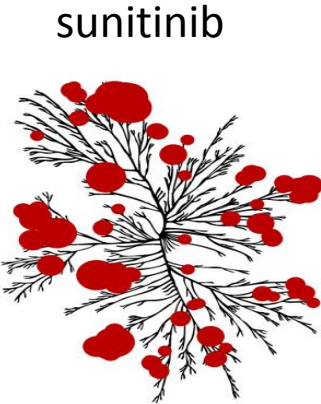
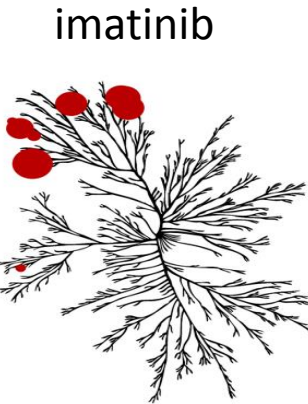
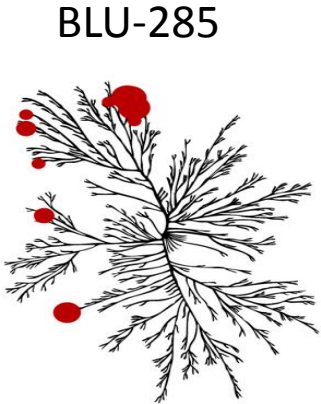
BLU-285
Activation loop open

BLU-285

*[chemical structure
for BLU-285 removed]*

BLU-285 is a potent, highly selective inhibitor of KIT and PDGFR α activation loop mutants

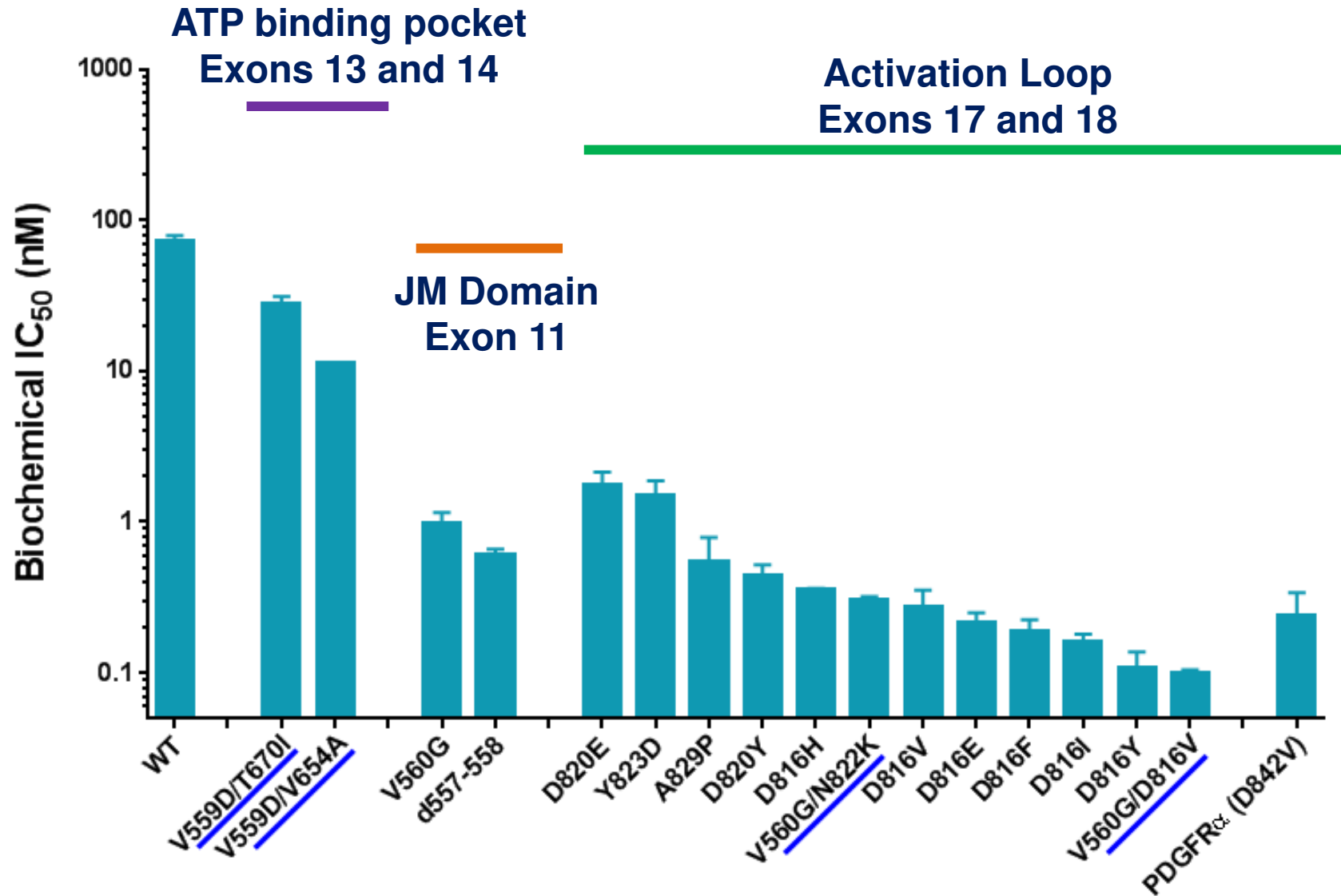
Compound	Activation loop		JM domain/ activation loop	
	Exon 18	Exon 17	Exon 11/17	
	PDGFR α D842V IC ₅₀ nM	KIT D816V IC ₅₀ nM	KIT V560G/D816V IC ₅₀ nM	
BLU-285	0.24	0.27	0.10	Type II inhibitors
imatinib	759	8150	6145	
sunitinib	120	207	97.2	
regorafenib	810	3640	1685	
midostaurin	4.9	2.8	1.4	Non-selective Type I inhibitors
crenolanib	0.2	1.5	1.2	



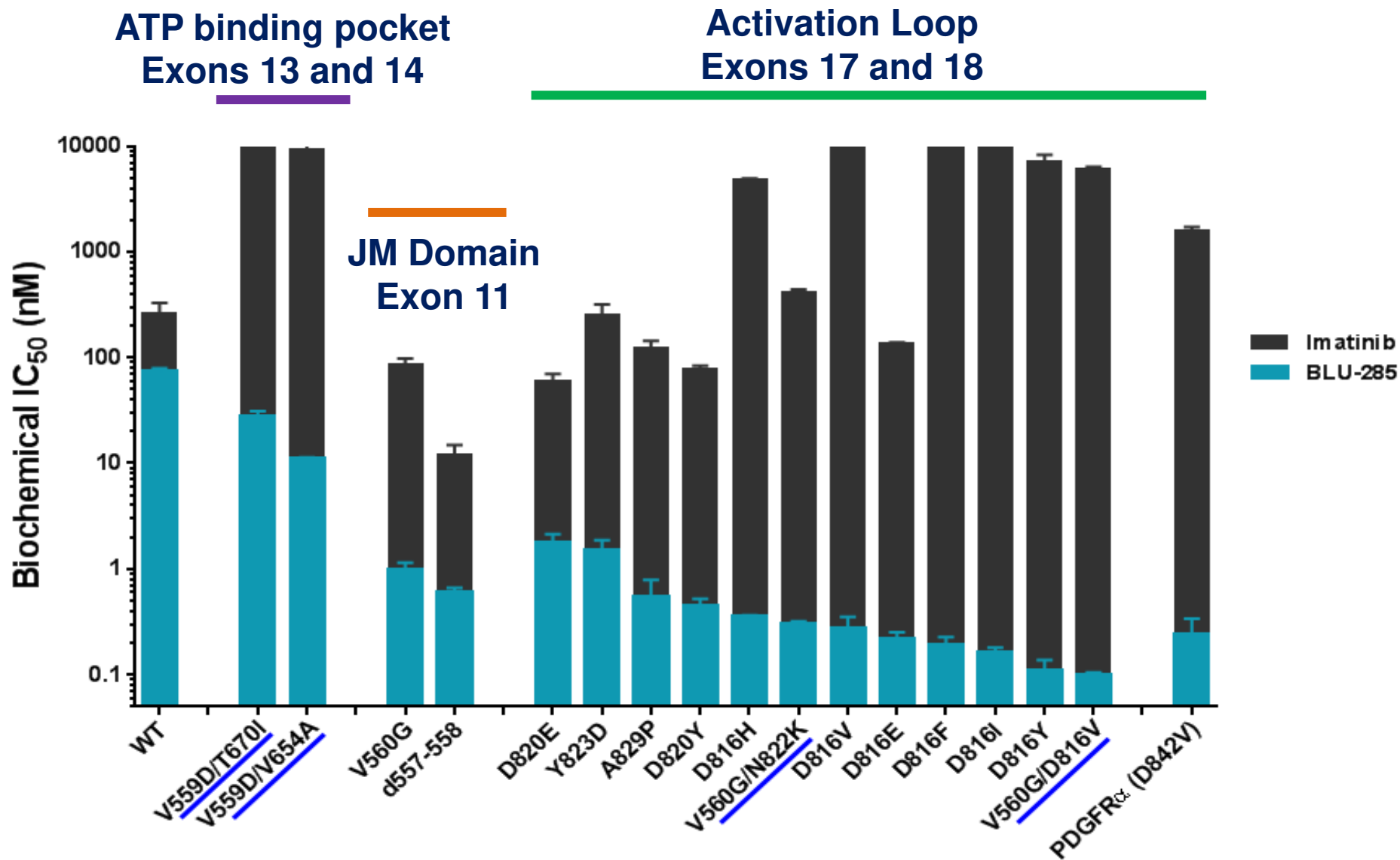
Kinome screening at 3 μ M

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

BLU-285 potently inhibits a broad spectrum of disease relevant KIT mutants

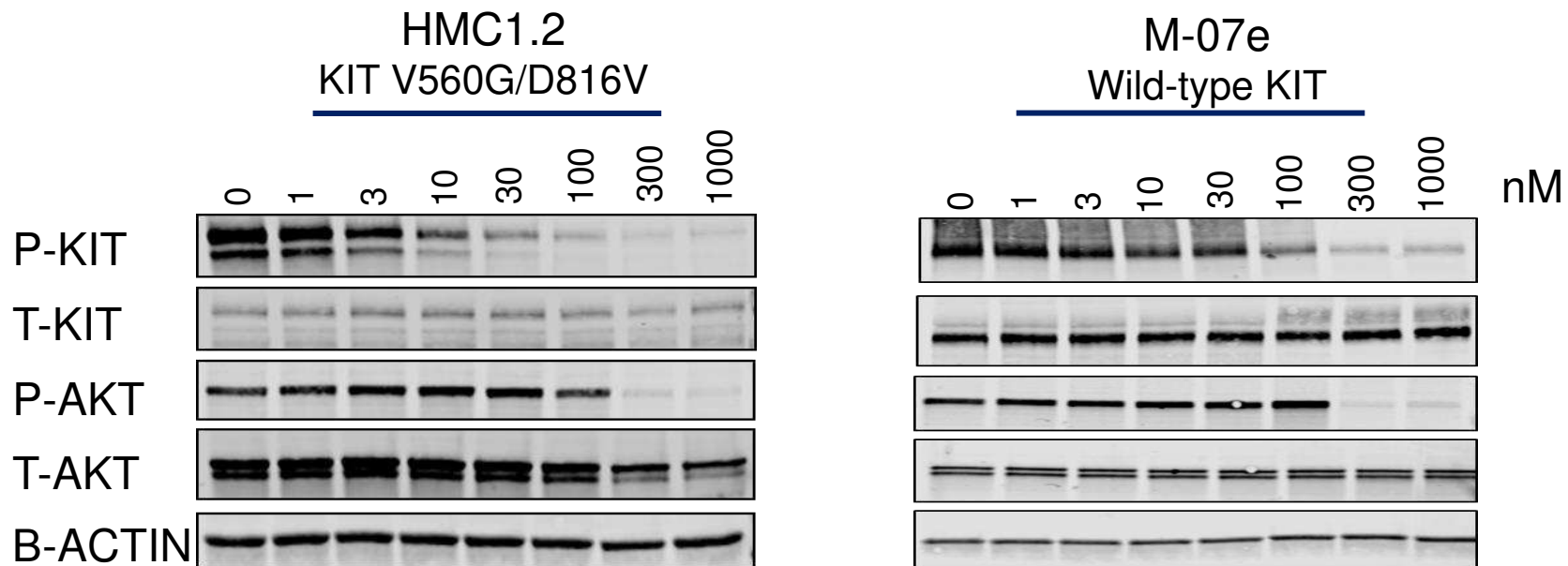


BLU-285 inhibits a broad spectrum of disease relevant KIT mutants more potently than imatinib

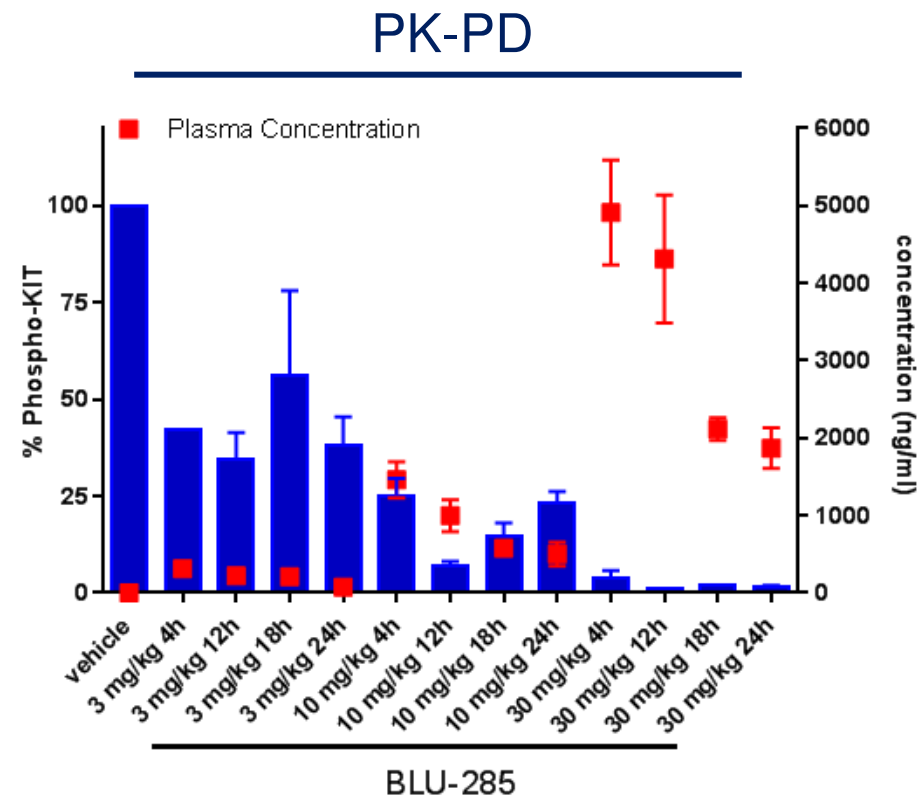
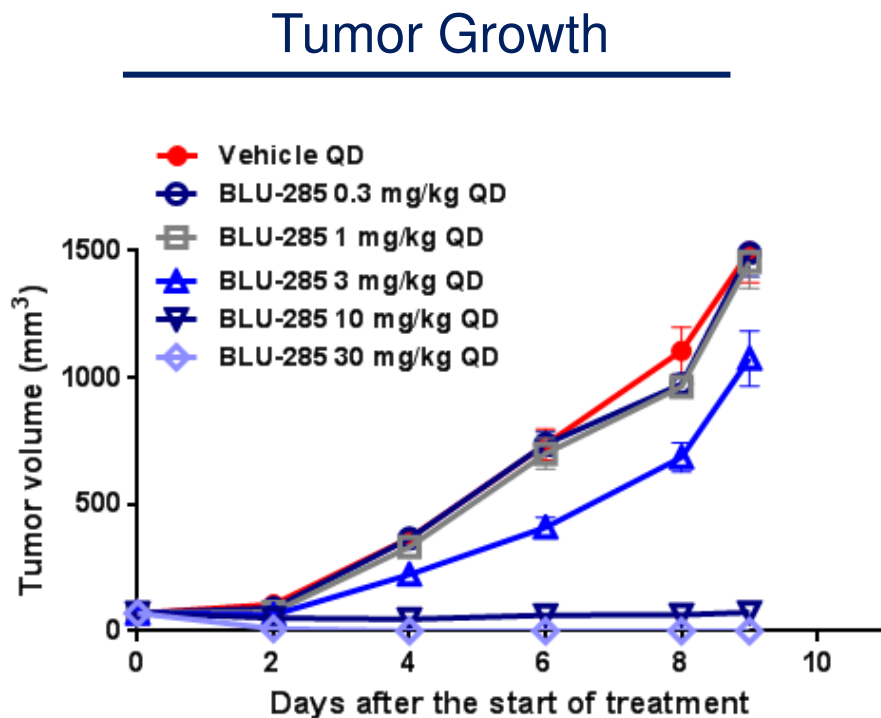


BLU-285 biochemical activity is recapitulated in cells

Cell Line	KIT mutation	Exon	Tissue	P-KIT inhibition	
				BLU-285	IC ₅₀ (nM) Imatinib
M-07e	Wild type	-	human megakaryoblastic leukemia	192	336
HMC1.1	V560G	11	human mast cell leukemia	100	31
Kasumi	N822K	17	human acute myeloid leukemia	40	126
P815	D816Y	17	murine mastocytoma	22	1235.6
HMC1.2	V560G/D816V	11/17	human mast cell leukemia	4	9143.5
CHO	PDGFR α D842V	18	engineered	30	3145



BLU-285 is active in a primary activation loop mutant in vivo model

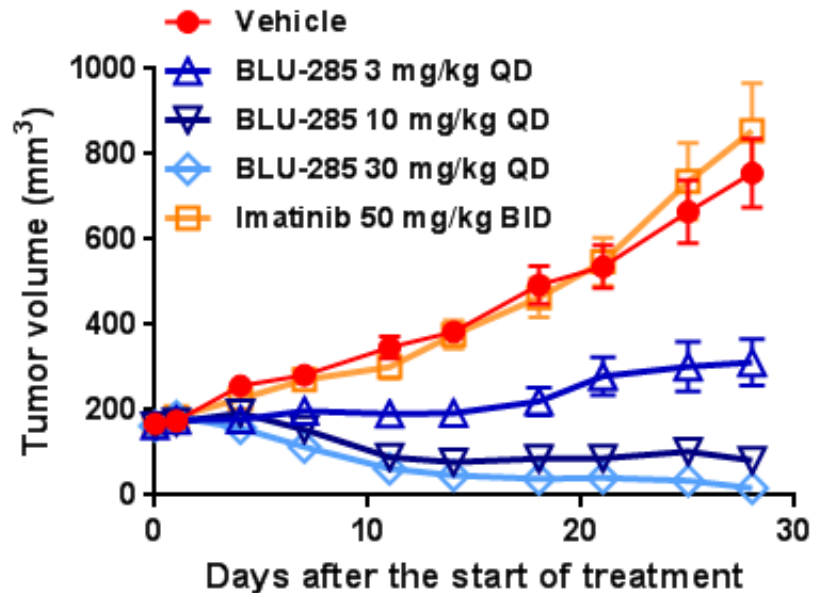


KIT Exon 17-driven P815 mastocytoma allograft:

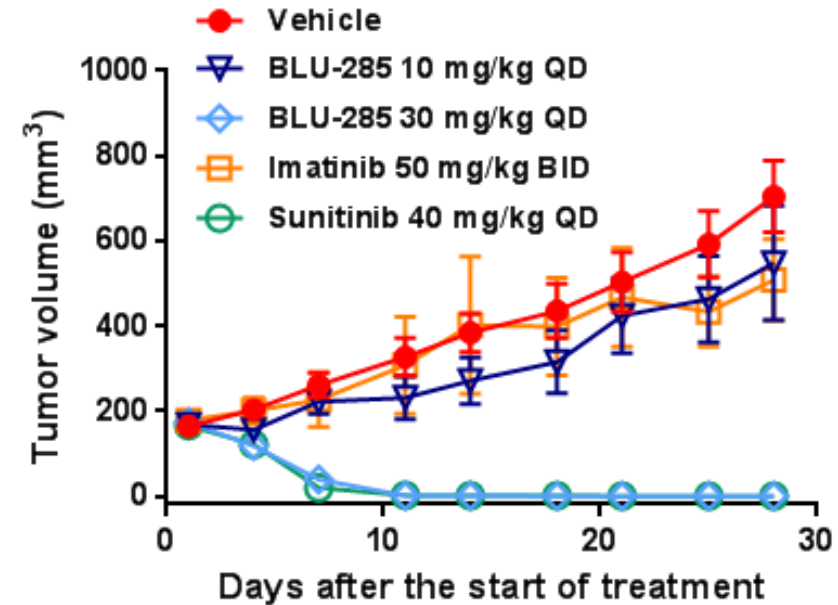
- Mutation in KIT exon 17 equivalent to human **KIT D816Y**
- Tumor regression observed with 10 and 30 mg/kg BLU-285 once daily, oral dosing
- BLU-285 well tolerated at all doses

BLU-285 is active in imatinib-resistant GIST PDX models

Tumor Growth
Exon 11/17 mutant GIST PDX



Tumor Growth
Exon 11/13 mutant GIST PDX



KIT Exon 11/17 mutant ([del556-558/Y823D](#)) GIST PDX:

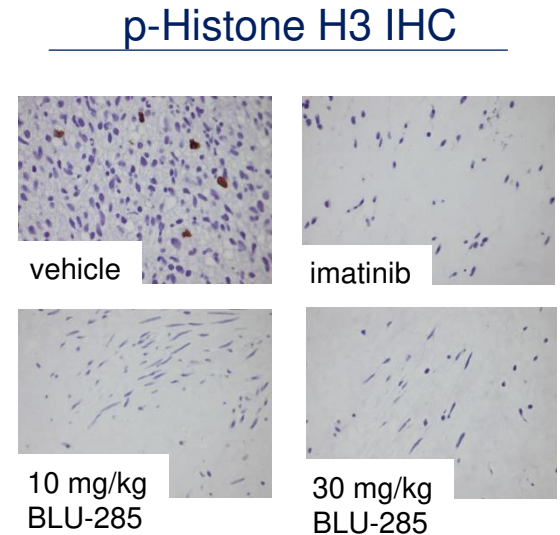
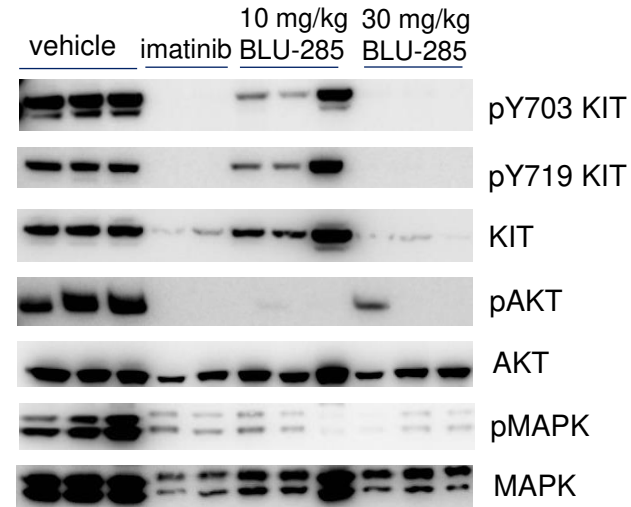
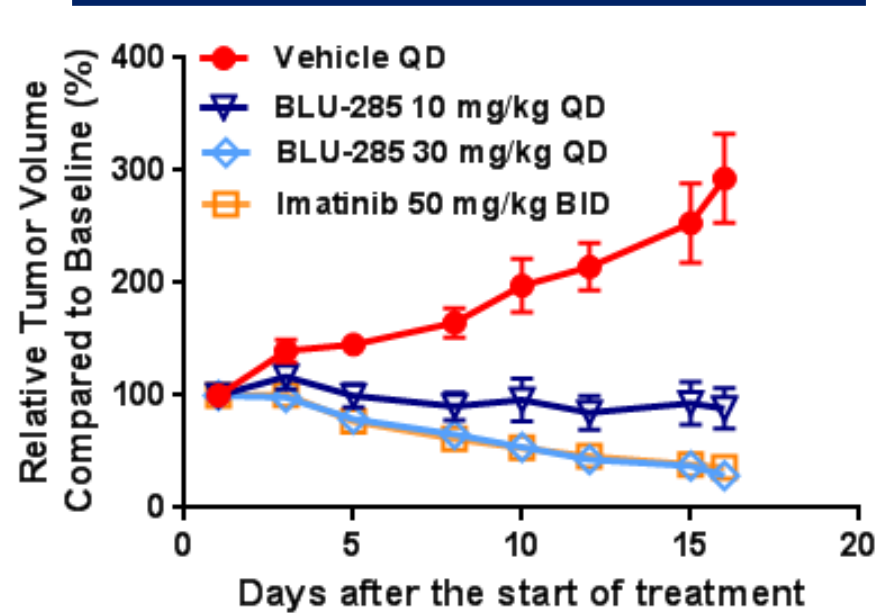
- Tumor regression observed with 10 and 30 mg/kg BLU-285

KIT Exon 11/13 mutant ([V559D/V654A](#)) GIST PDX:

- Tumor regression observed with 30 mg/kg BLU-285

BLU-285 is active in a primary exon 11 mutant GIST PDX model

Tumor Growth Exon 11 mutant GIST PDX



KIT Exon 11 mutant ([del557-559insF](#)) GIST PDX:

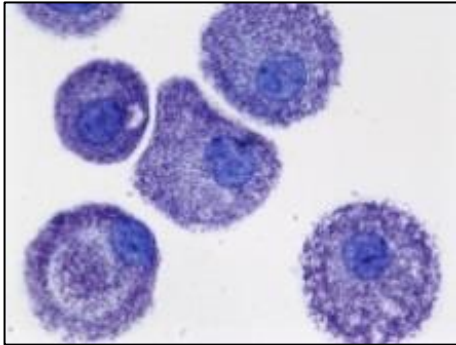
- Tumor regression observed with 30 mg/kg BLU-285, stasis with 10 mg/kg BLU-285 once daily, oral dosing
- BLU-285 active against primary KIT exon 11 mutants, suggests reemergence of primary clone is unlikely
- Collaboration with P. Schoffski, (KU Leuven) Abstract #687 Monday April 3, 1- 5pm.

BLU-285 Achieves Rapid Clinical Proof of Concept in Diseases Driven by KIT/PDGFR α Mutants

KIT D816V is a key driver in 90-95% of systemic mastocytosis

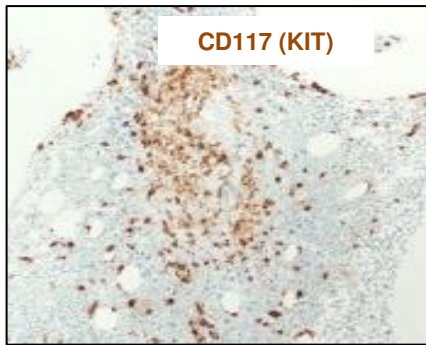
- Advanced systemic mastocytosis is a rare and severe disease that shortens life expectancy with a wide range of debilitating symptoms and organ damage

Blood



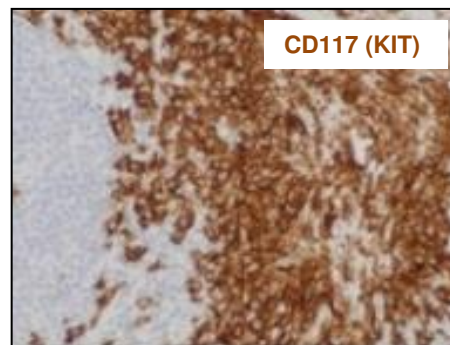
MC degranulation
MC mediator Sx
↑tryptase

Bone and bone marrow



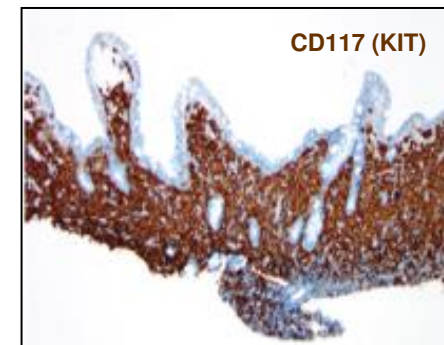
Osteolytic bone lesions
Cytopenias

Liver and Spleen



Liver function abnormalities,
Ascites, or Hypersplenism

GI tract



Hypoalbuminemia
Weight loss

Skin



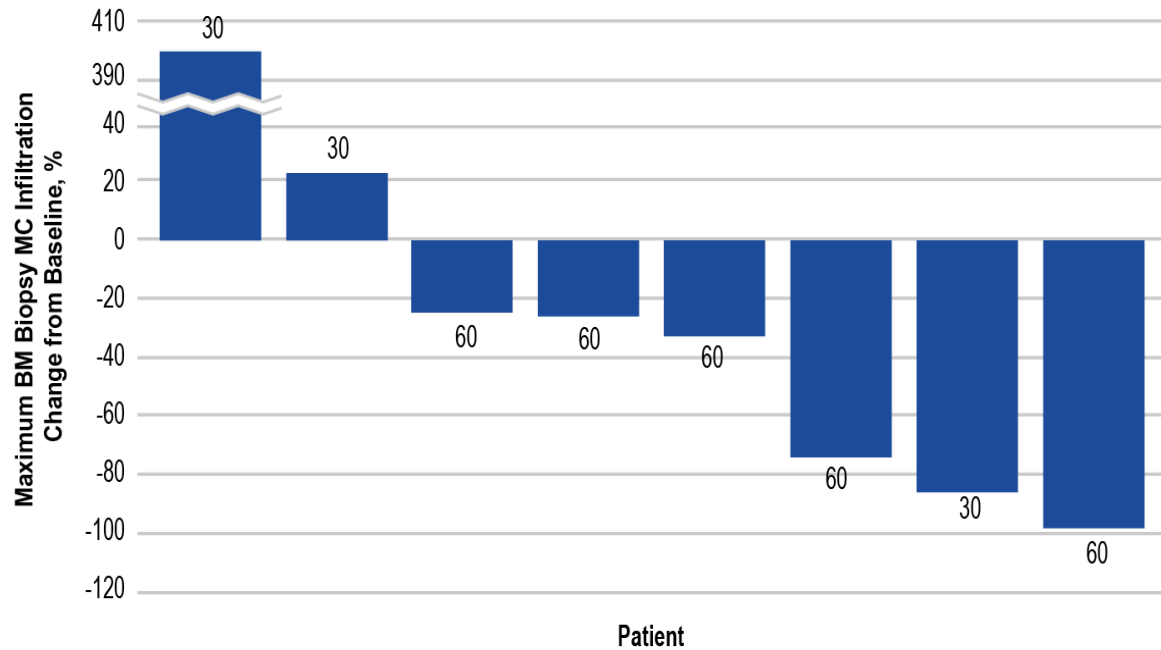
Urticaria
pigmentosa

C-findings

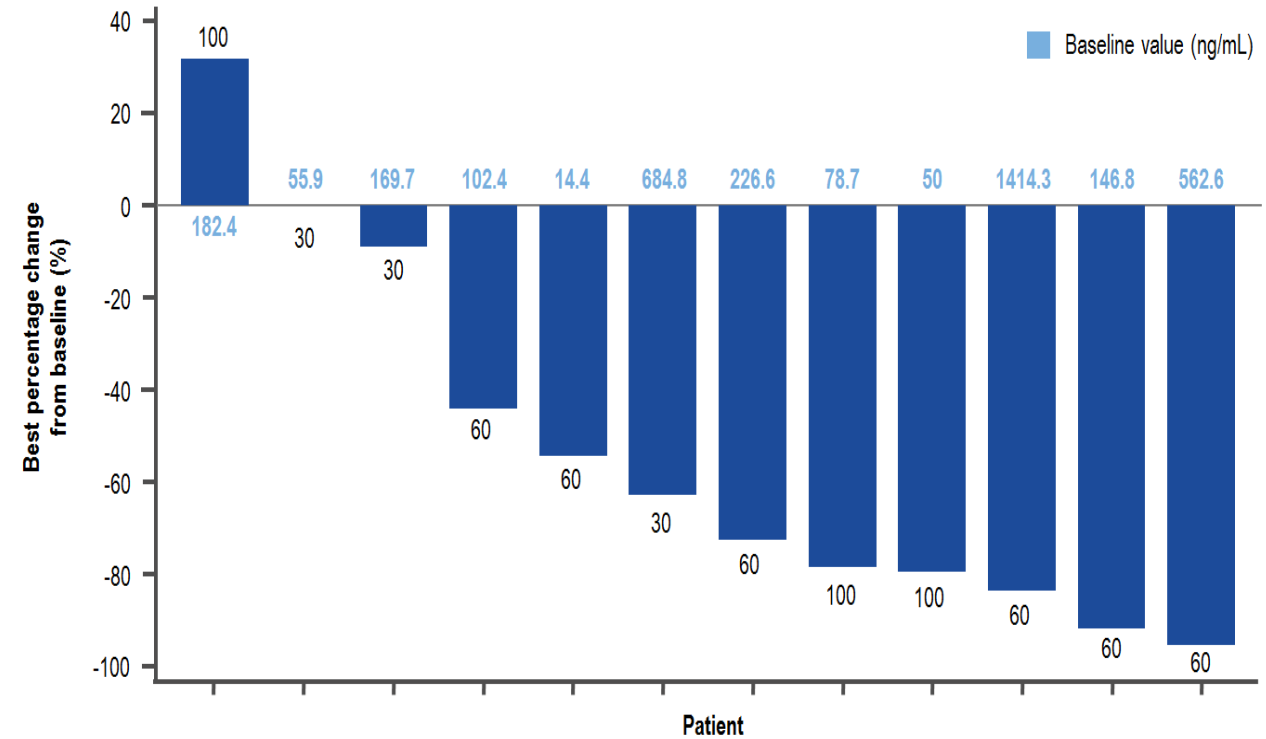
Encouraging clinical activity in phase 1 AdvSM study

Objective decreases in mast cell burden and serum tryptase

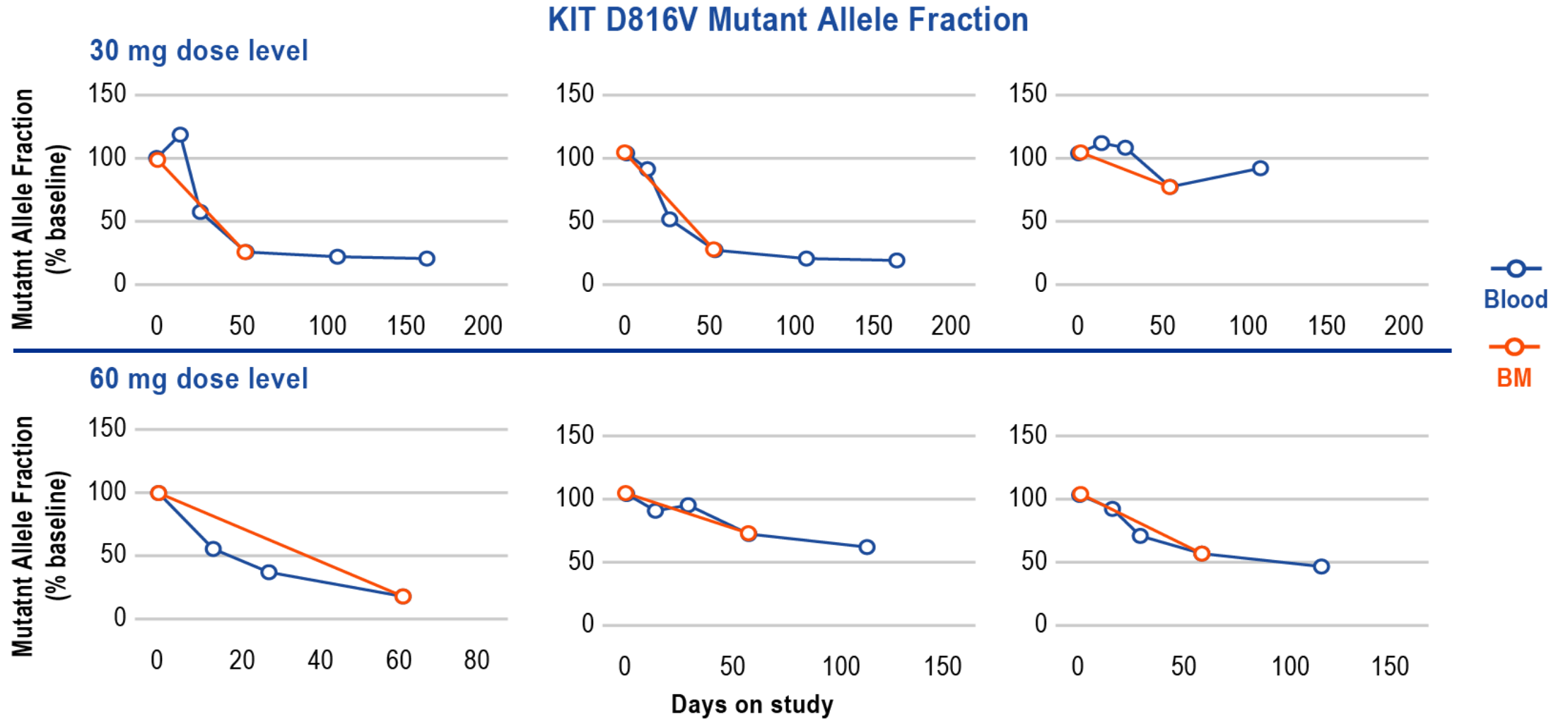
Decreased bone marrow mast cells in 6 of 8 patients



Decreased serum tryptase in 10 of 12 patients



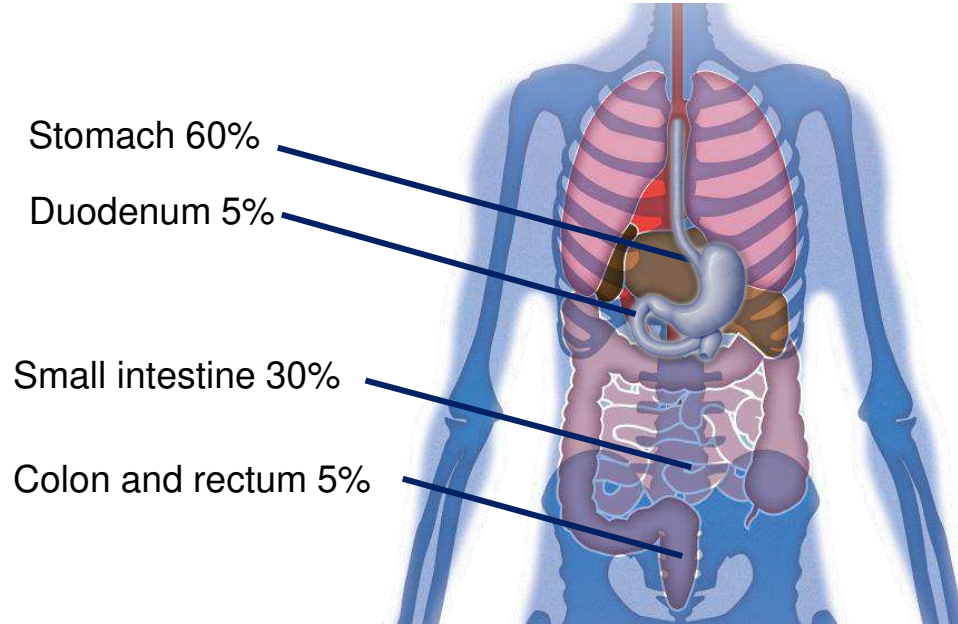
Molecular response observed in blood and bone marrow of SM patients treated with BLU-285



Droplet digital PCR with allele specific primers measures KIT D816V allele burden in blood and BM aspirate

Activating KIT or PDGFR α mutations drive metastatic GIST

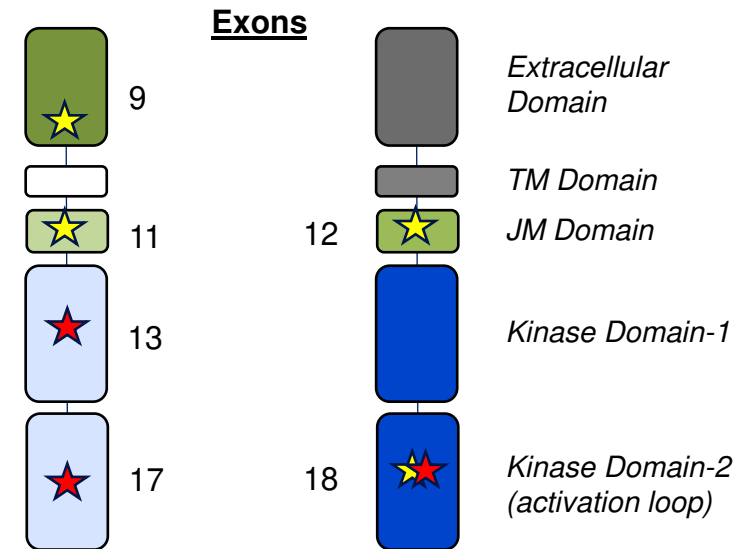
Most common GI sarcoma



- Cancer of the interstitial cells of Cajal
- Chemotherapy has no impact

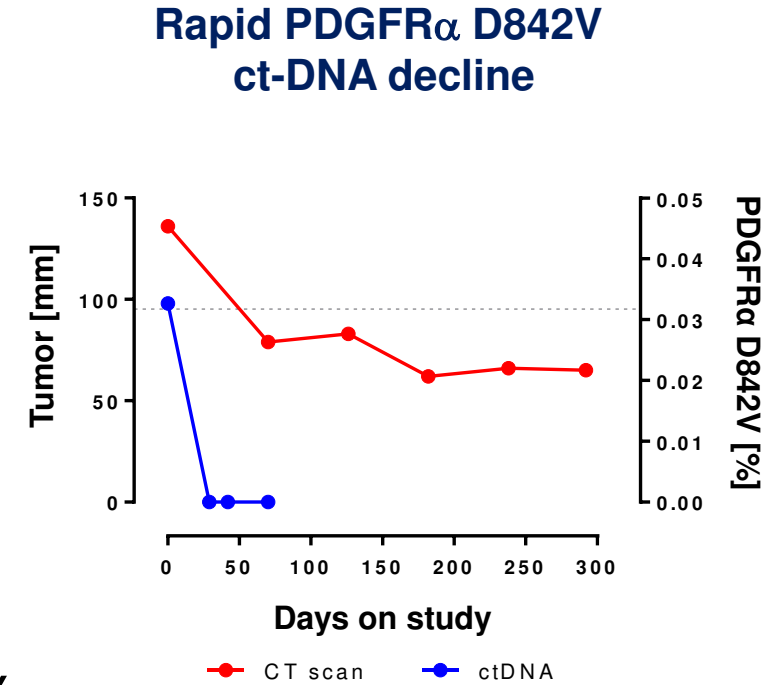
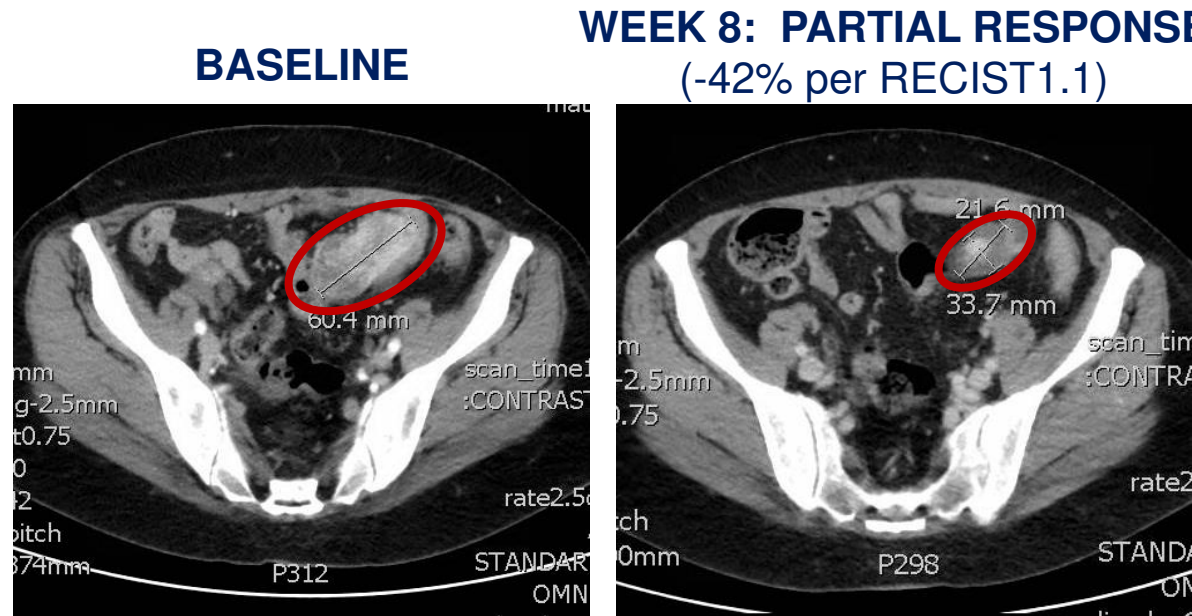
KIT ~ 80%

PDGFR α ~ 8%



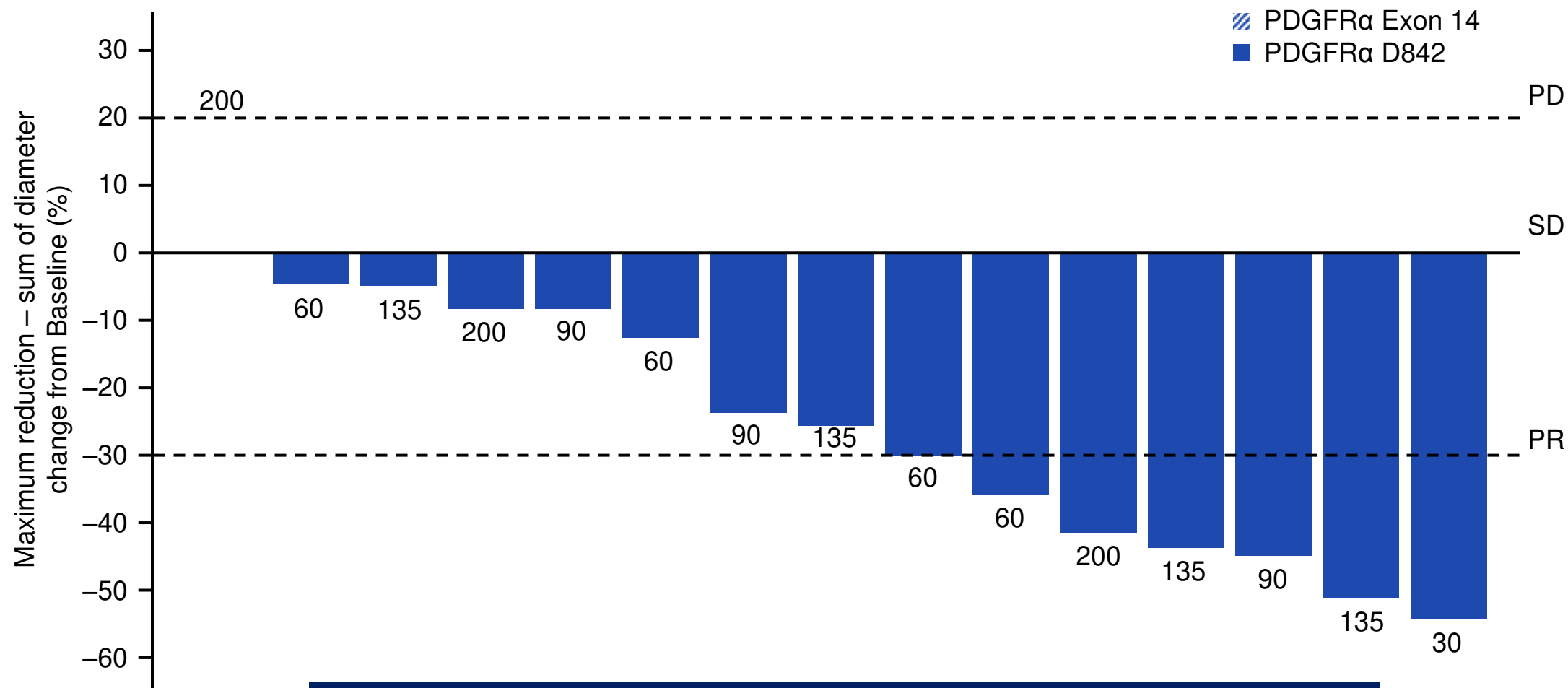
- Primary mutational hotspots ★
 - KIT Exons 9 or 11
 - PDGFR α Exons 12 and 18 (D842V)
- Resistance mutations ★
 - KIT Exons 13 and 17
 - PDGFR α Exon 18 (D842V)

Radiographic response per RECIST 1.1 in PDGFR α D842V GIST in phase 1 testing (dose level 1, 30 mg)



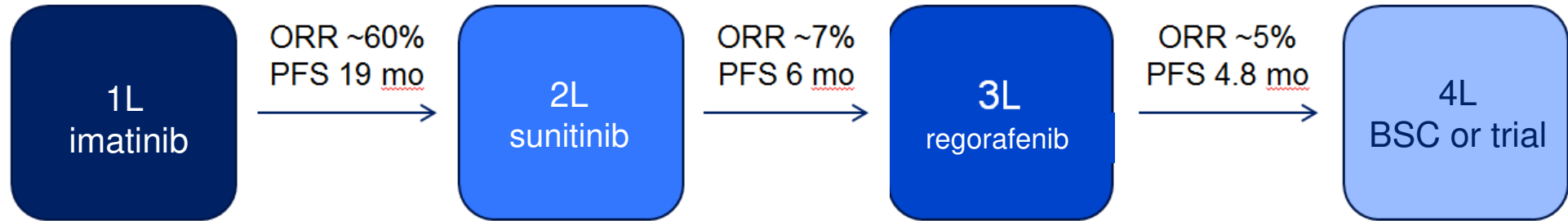
- *65 year old female, Primary Gastric GIST, PDGFR α D842V*
 - Previous surgical de-bulking: stomach; peritoneal metastases x 2; colon
 - Prior response to crenolanib followed by progression
 - Progression on prior dasatinib (no response)
 - Ongoing at Cycle 13 with confirmed partial response (-52% per RECIST1.1)

Strong clinical activity against PDGFR α D842-mutant GIST at all dose levels



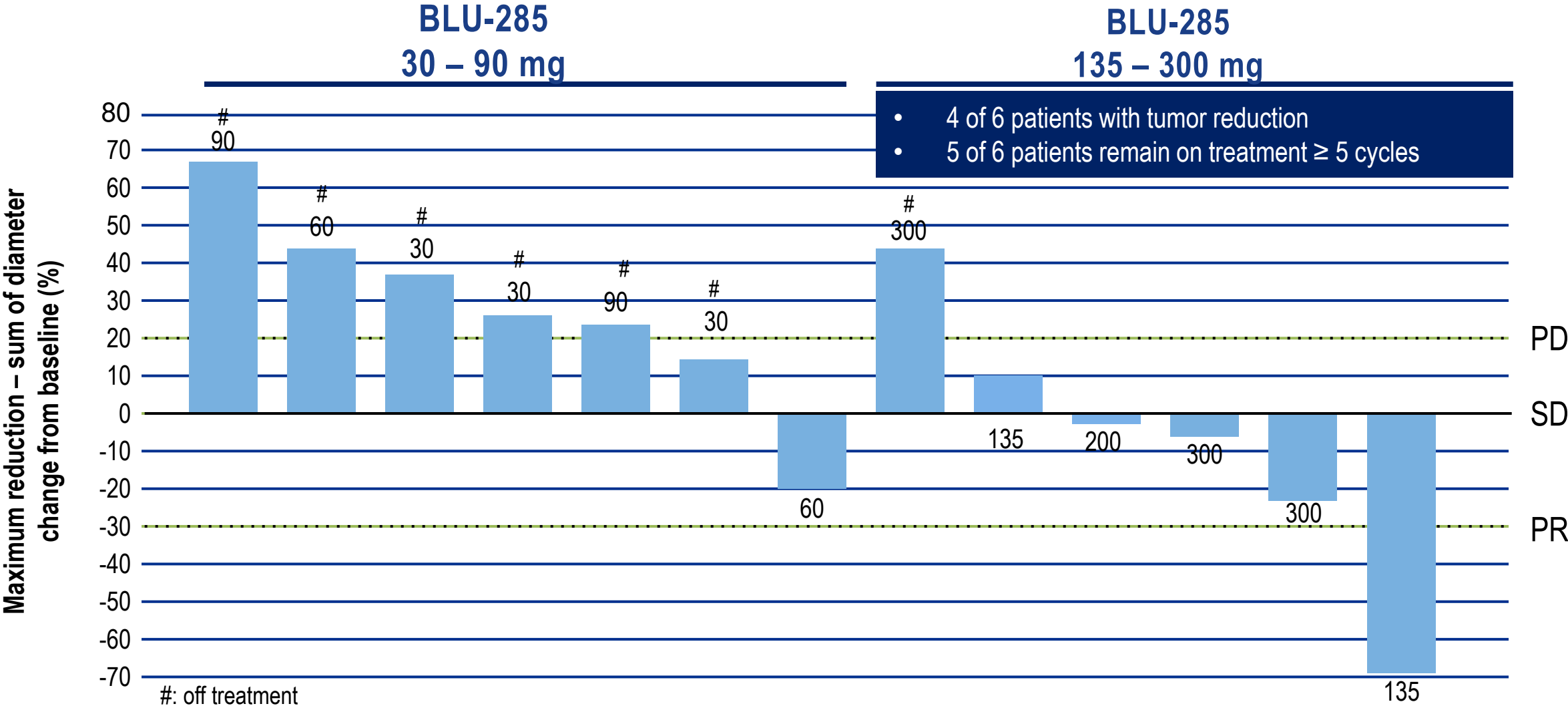
- 14 out of 14 D842-mutant patients with tumor reductions
- ORR = 42%, DCR = 100%

Imatinib/sunitinib-resistant GIST are enriched for KIT exon 17 mutants



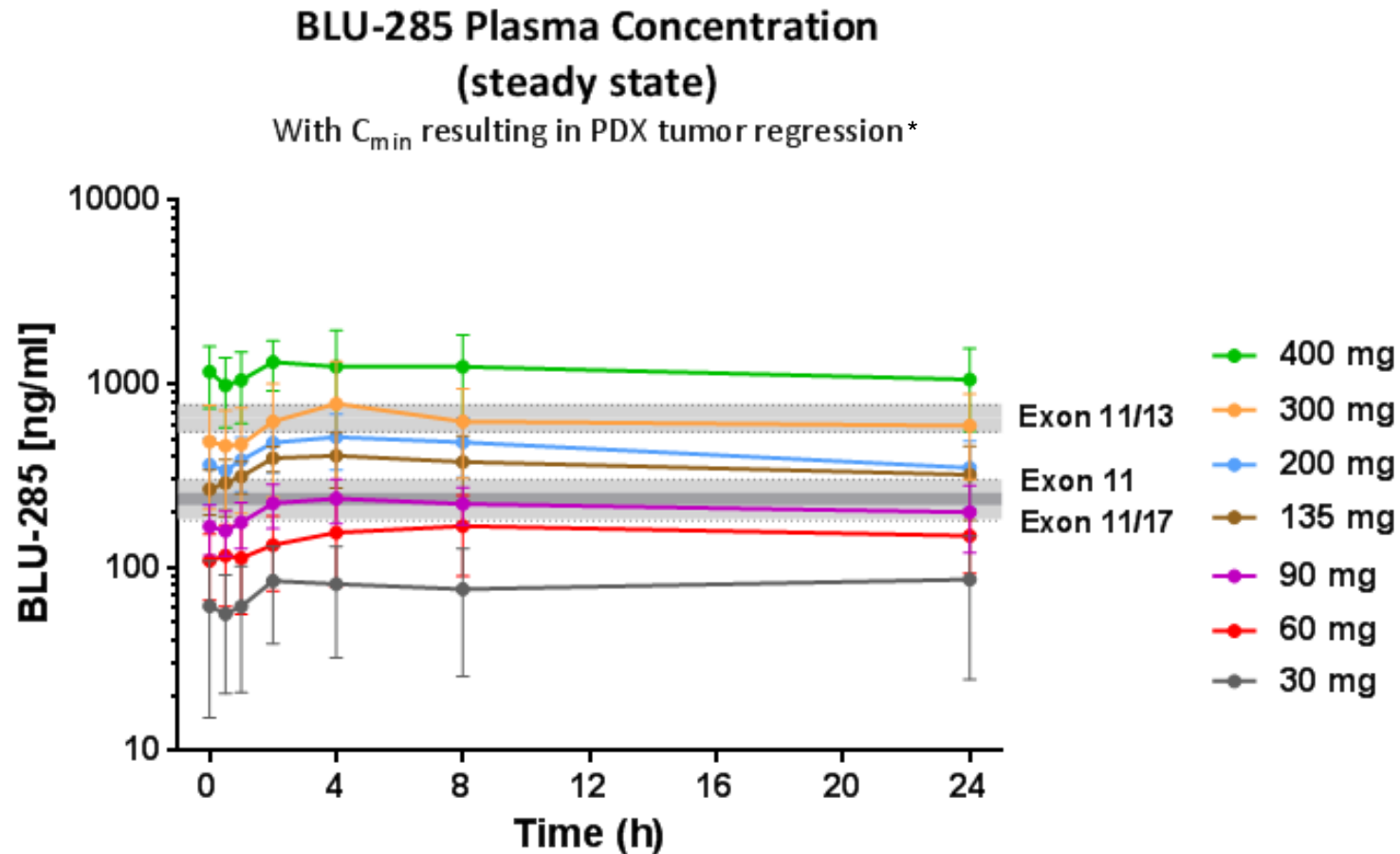
KIT Exon	1L imatinib	2L sunitinib	3L regorafenib
Exon 9	9%		
Exon 11	67%		
Exon 13		60-70%	
Exon 14			
Exon 17	1%	20%	90%
Exon 18			

Significant anti-tumor activity in TKI-resistant KIT-driven GIST at higher doses



BLU-285 demonstrates dose dependent human pharmacokinetics

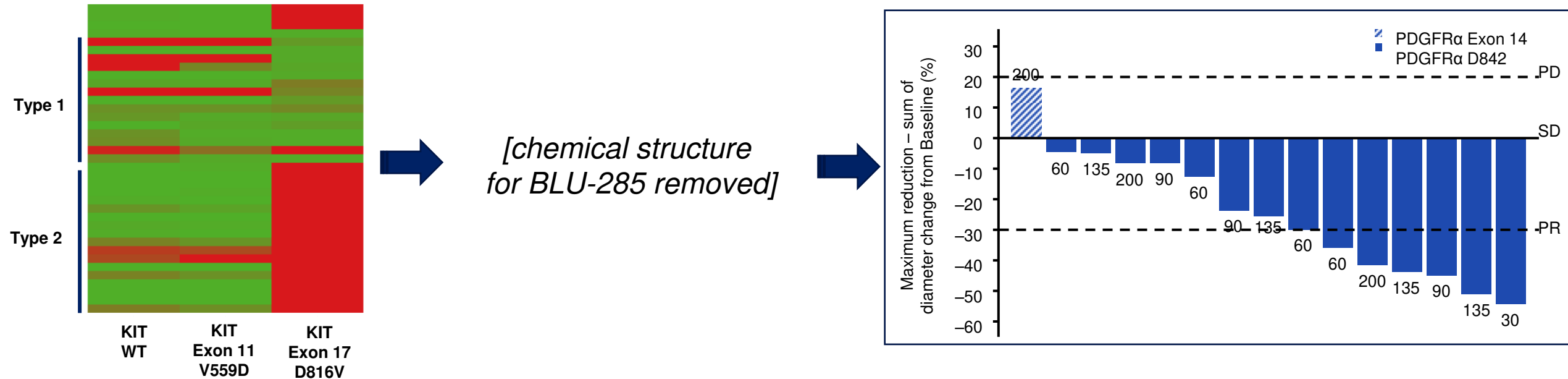
PDX studies suggest clinical exposures in therapeutic range



- PDX data suggest active dose range for KIT mutant GIST at levels ≥ 135 mg
- Expansion cohorts for GIST phase 1 trial recently initiated with RP2D of 400 mg QD

*Exposures adjusted for free fraction

In summary, mechanistic and structural understanding of disease-driving mutations paired with tailored inhibitors can accelerate drug development



- KIT/PDGFRα activation loop mutants are unaddressed by approved therapies
- Insights from BMC library catalyzed design of BLU-285, a potent, highly-selective type 1 inhibitor of KIT/PDGFRα activating mutants
- Potent activity of BLU-285 on KIT/PDGFR activation loop mutants has informed initial clinical development strategy resulting in early clinical proof of concept in several patient populations

Acknowledgements

- **Thanks to all participating patients and their families**
- **Thanks to all study investigators, nurses and research coordinators**
 - Abramson Cancer Center at the University of Pennsylvania
 - Dana-Farber Cancer Institute
 - Fox Chase Cancer Center
 - MD Anderson Cancer Center
 - Oregon Health & Science University
 - Stanford University
 - University of Colorado
 - University of Michigan Comprehensive Cancer Center
 - University of Utah, Huntsman Cancer Institute
 - Centre Leon Berard
 - Erasmus MC Cancer institute
 - Gartnavel General Hospital, Beatson West of Scotland Cancer Center
 - Guy's & St Thomas NHS Trust
 - Institut Gustave Roussy
 - Leuven Cancer Institute
 - Royal Marsden Hospital / Institute for Cancer Research
 - University of Essen
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 - Patrick Schöffski (Leuven Cancer Institute)
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