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

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New Drugs on the Horizon

2017 AACR Annual Meeting

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Disclosures

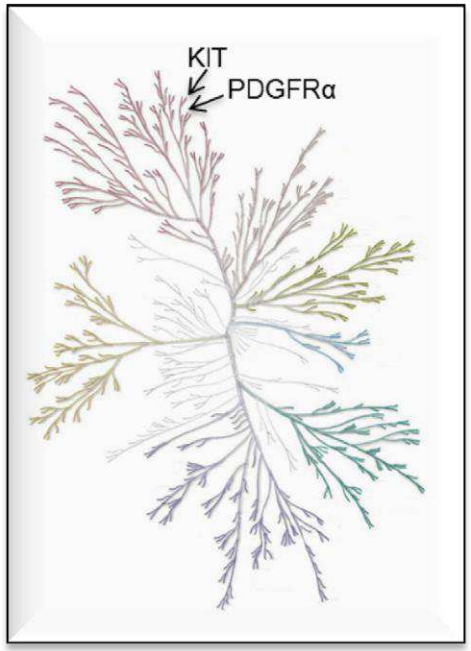
- Employee and shareholder of Blueprint Medicines
- BLU-285 is an investigational agent currently in development by Blueprint Medicines

Activating mutations in KIT and PDGFRα are disease drivers

KIT and PDGFRα

- Highly-related class III receptor tyrosine kinases
- Kinase activity normally requires ligand-induced dimerization

- PDGFRα activity: organogenesis, angiogenesis, vascular integrity
- KIT activity: hematopoeisis, melanocytes, germ cells



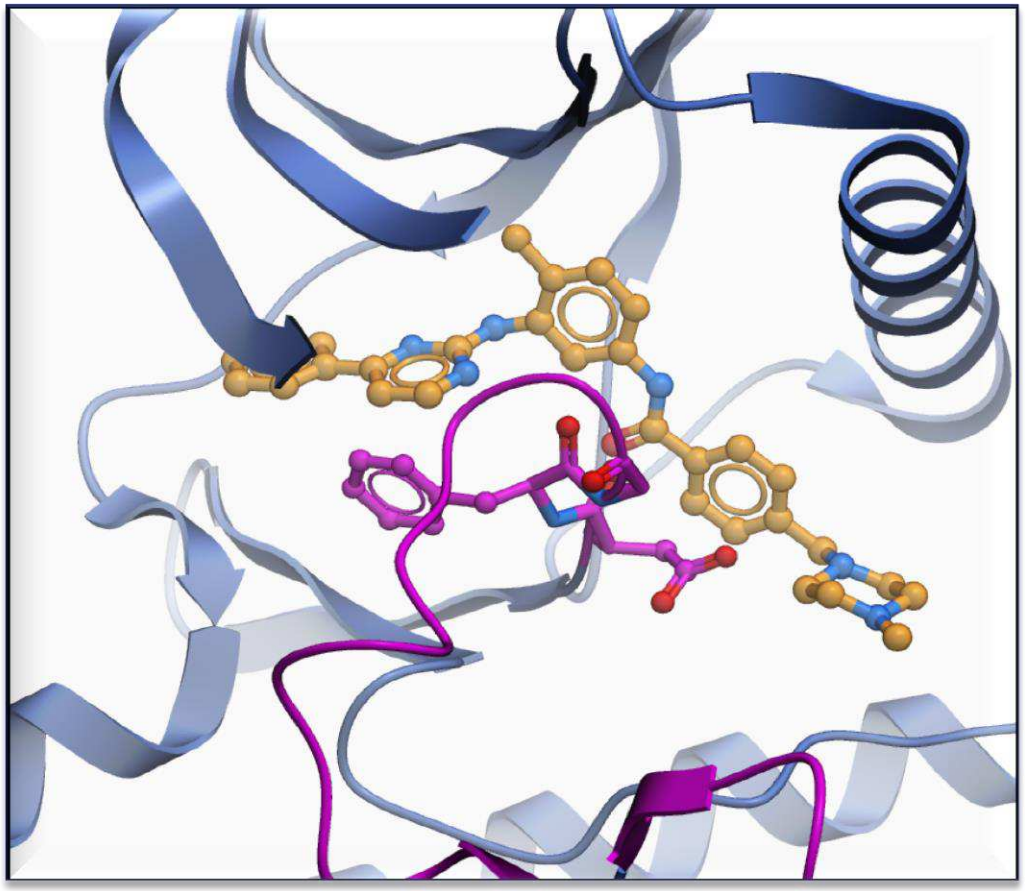
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

Mutation	Disease
PDGFRα Fusion	MDS, MPN, Eosinophilic leukemia
PDGFRα Exon 12	GIST
PDGFRα 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

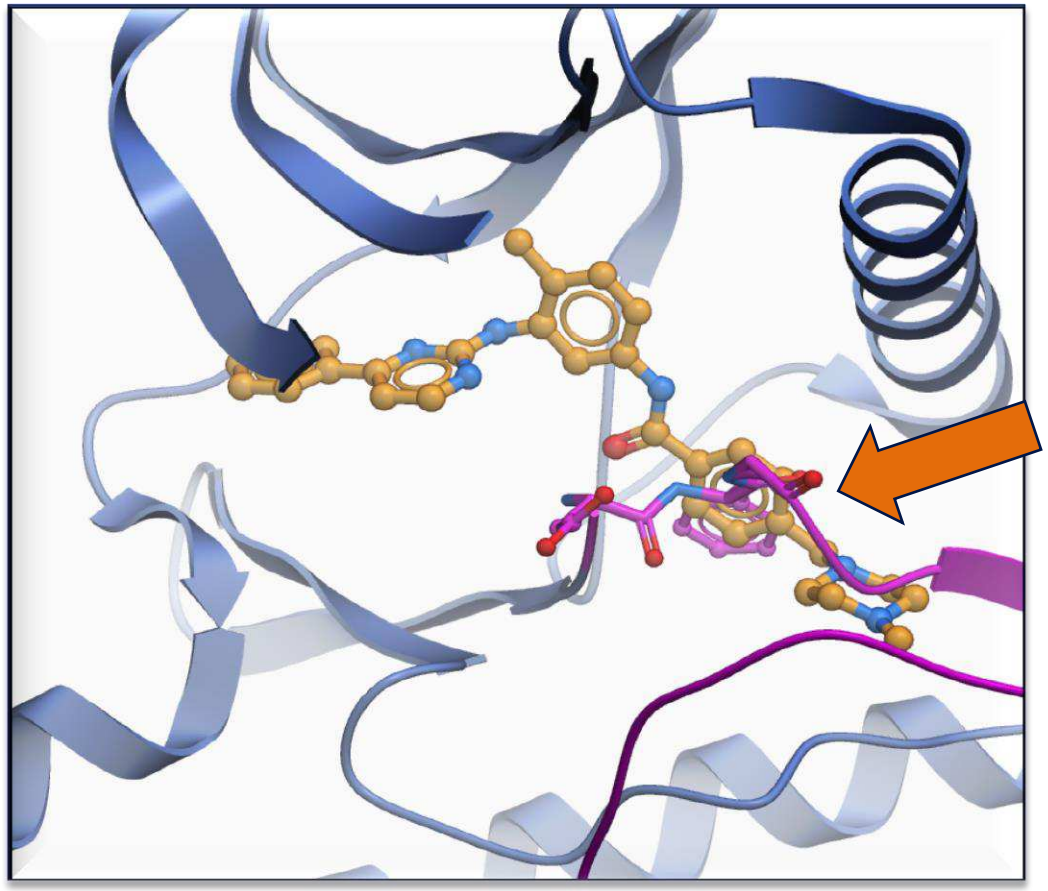
imatinib-sensitive

KIT activation loop mutations abrogate type II inhibitor binding

Imatinib binds inactive conformation of KIT/PDGFRα



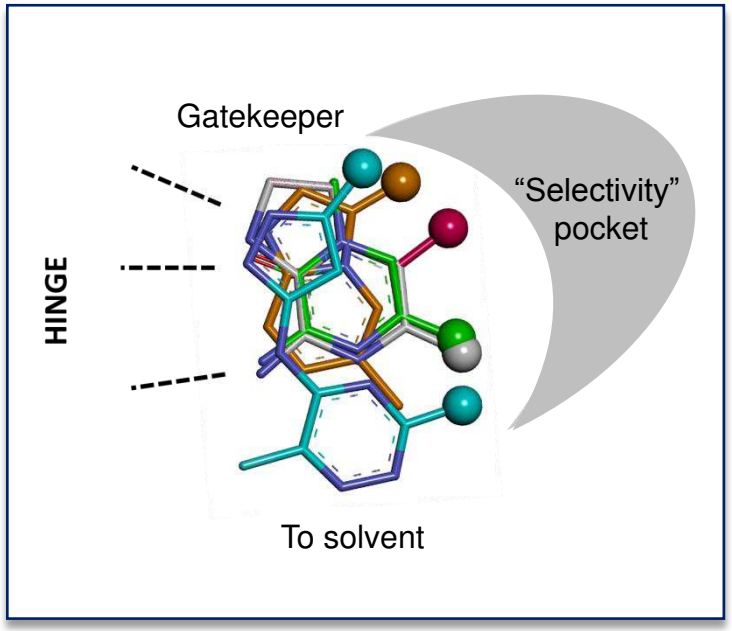
Inactive conformation
Activation loop closed, DFG-out
Type II inhibitors active



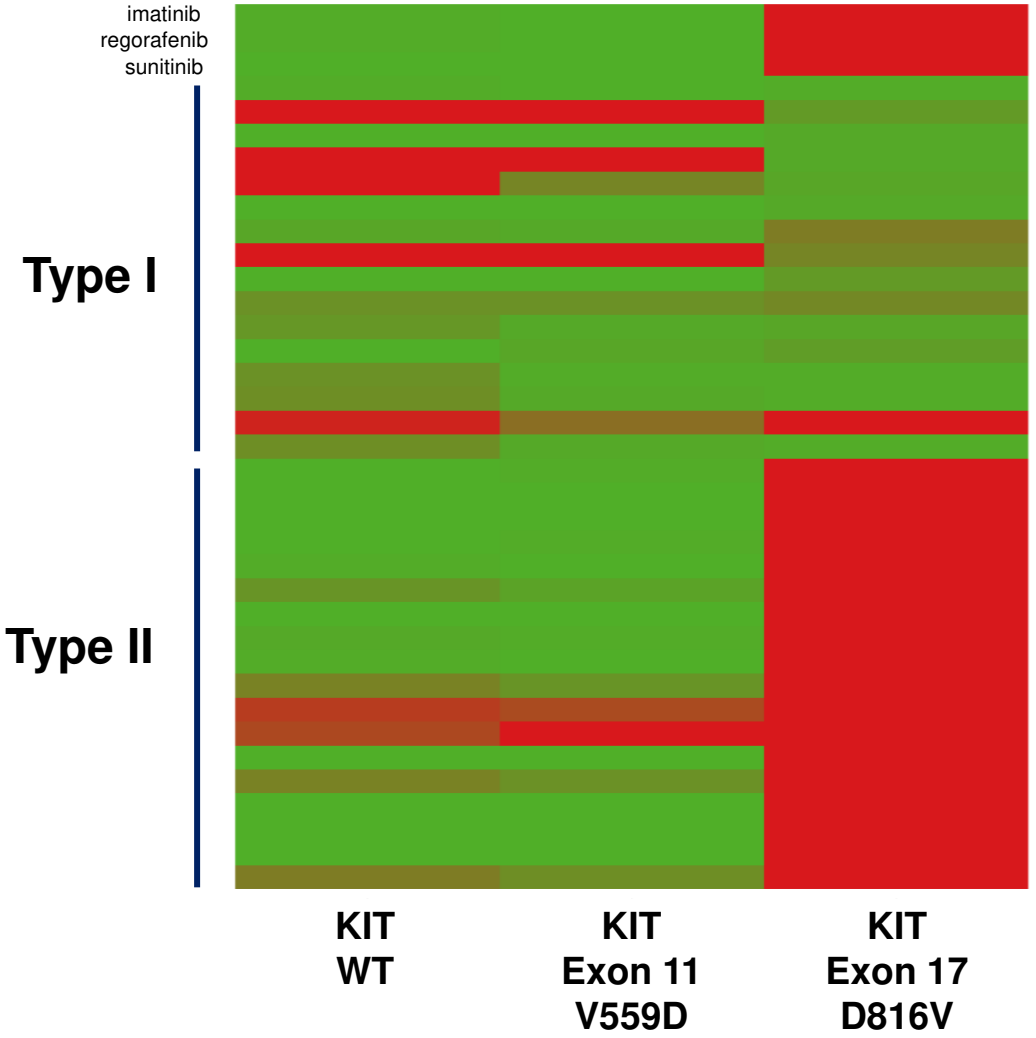
Active conformation
Activation loop open, DFG-in
Type II inhibitors inactive

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

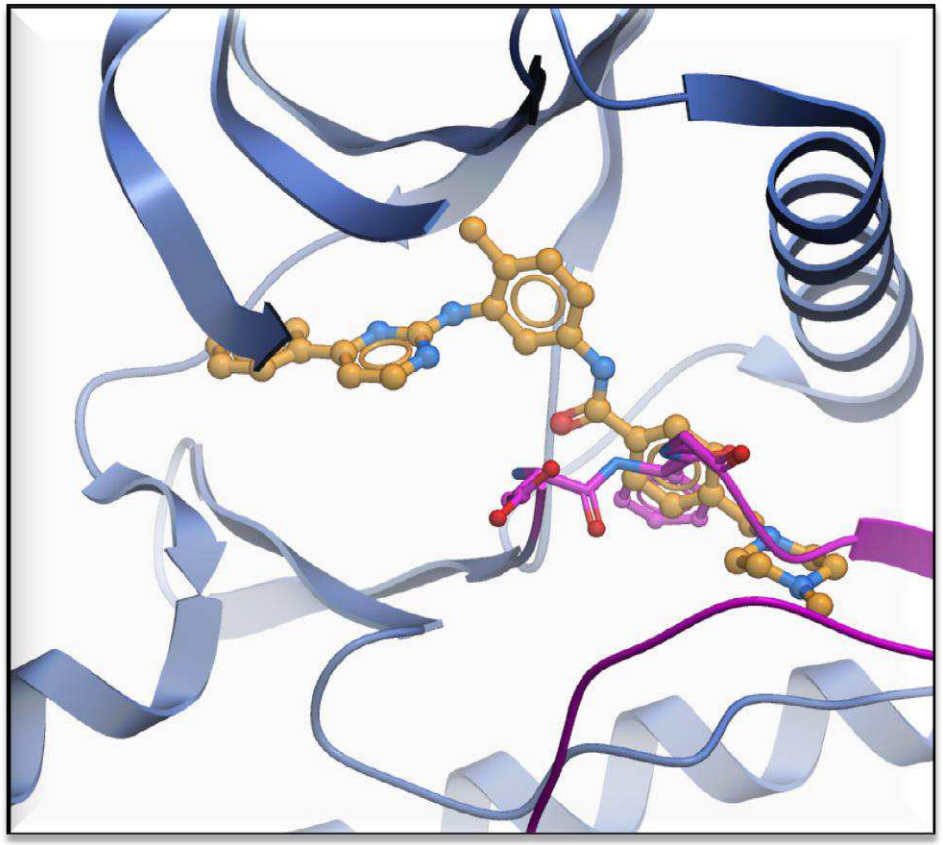
UNIQUE KINASE-DIRECTED COMPOUND LIBRARY



- **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/PDGFRα inhibitor that binds to the active conformation of the kinase



Imatinib
Activation loop open

BLU-285

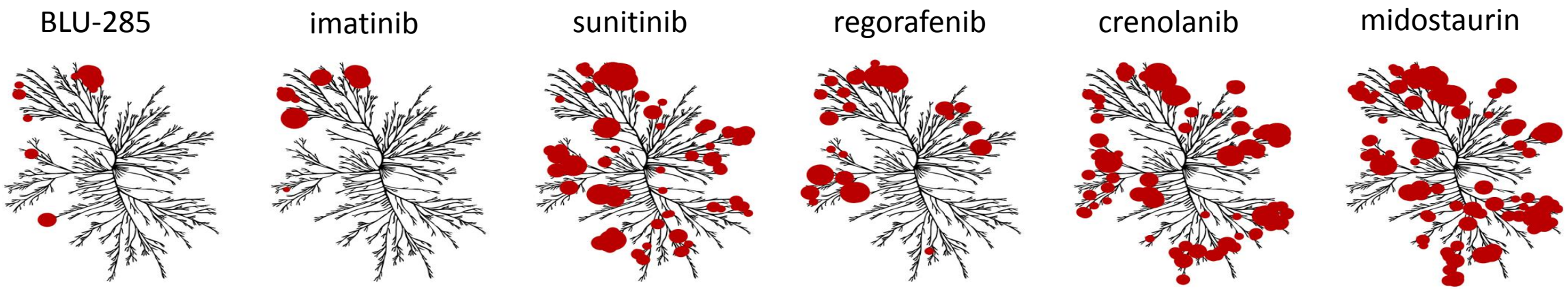
[chemical structure for BLU-285 removed]

BLU-285
Activation loop open

[chemical structure for BLU-285 removed]

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

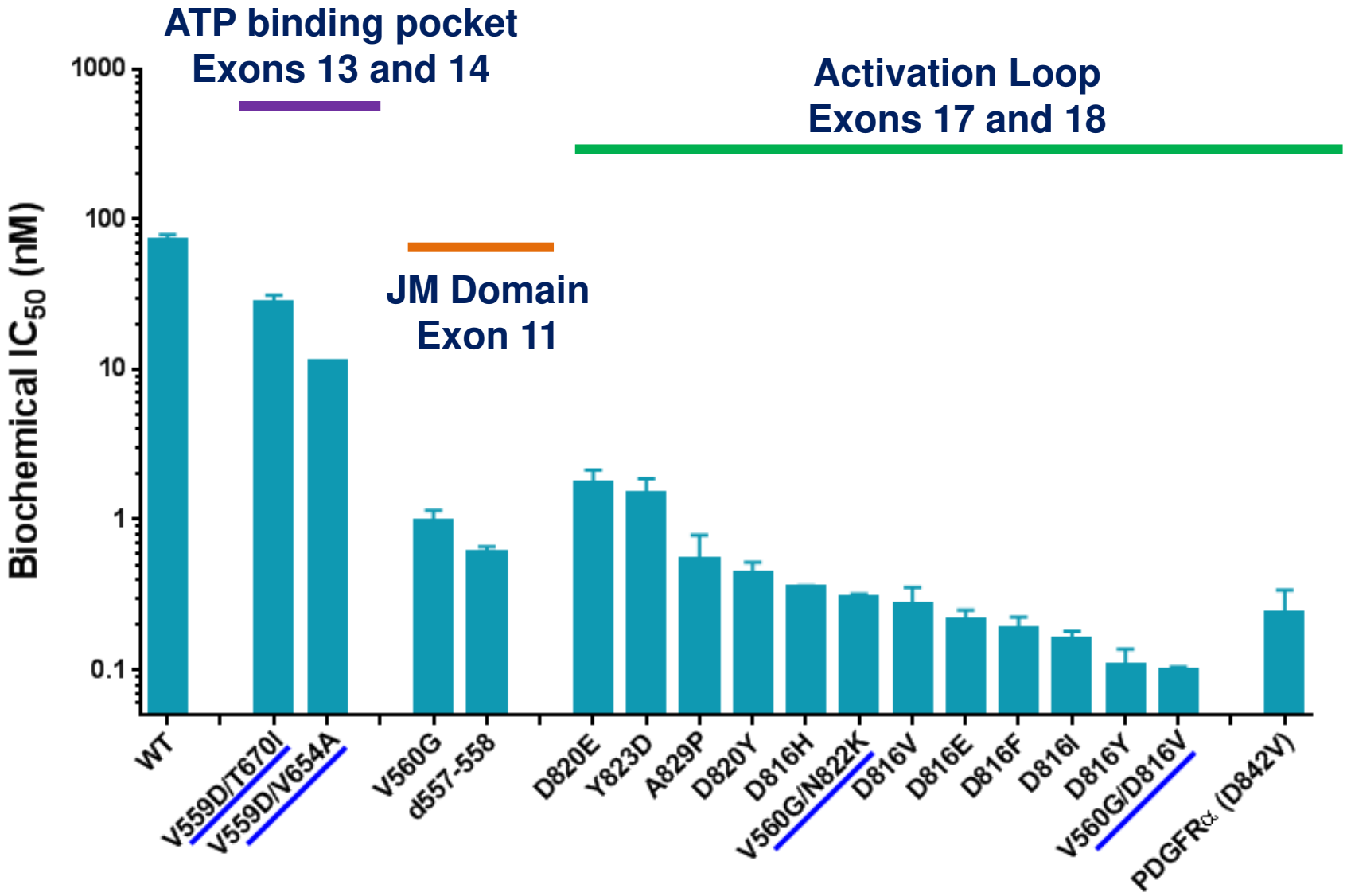
	Activation loop		JM domain/ activation loop	
	Exon 18	Exon 17	Exon 11/17	
Compound	PDGFRα D842V IC_{50} nM	KIT D816V IC_{50} nM	KIT V560G/D816V IC_{50} nM	
BLU-285	0.24	0.27	0.10	
imatinib	759	8150	6145	Type II inhibitors
sunitinib	120	207	97.2	
regorafenib	810	3640	1685	
midostaurin	4.9	2.8	1.4	Non-selective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



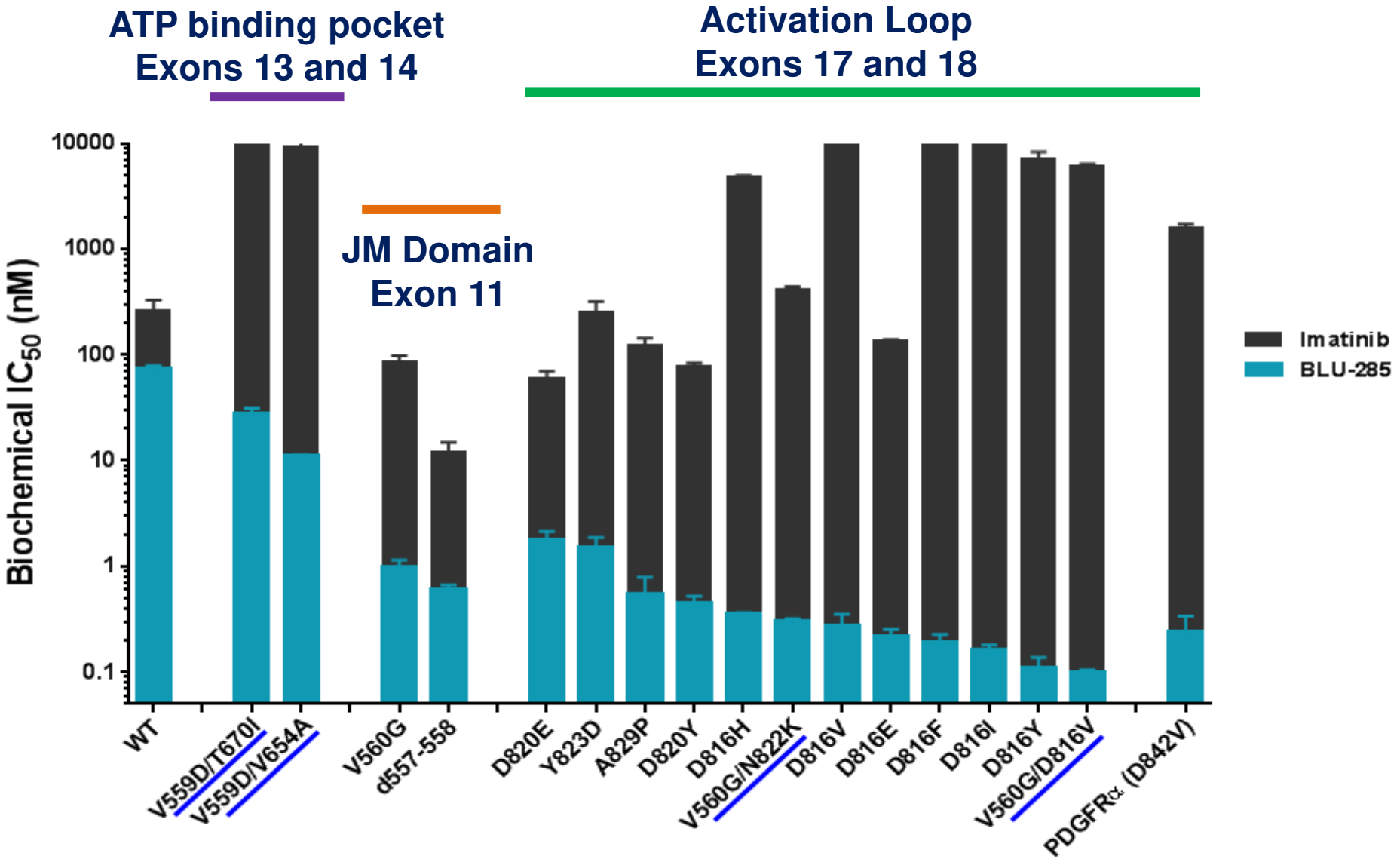
Kinome screening at 3 µM

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

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

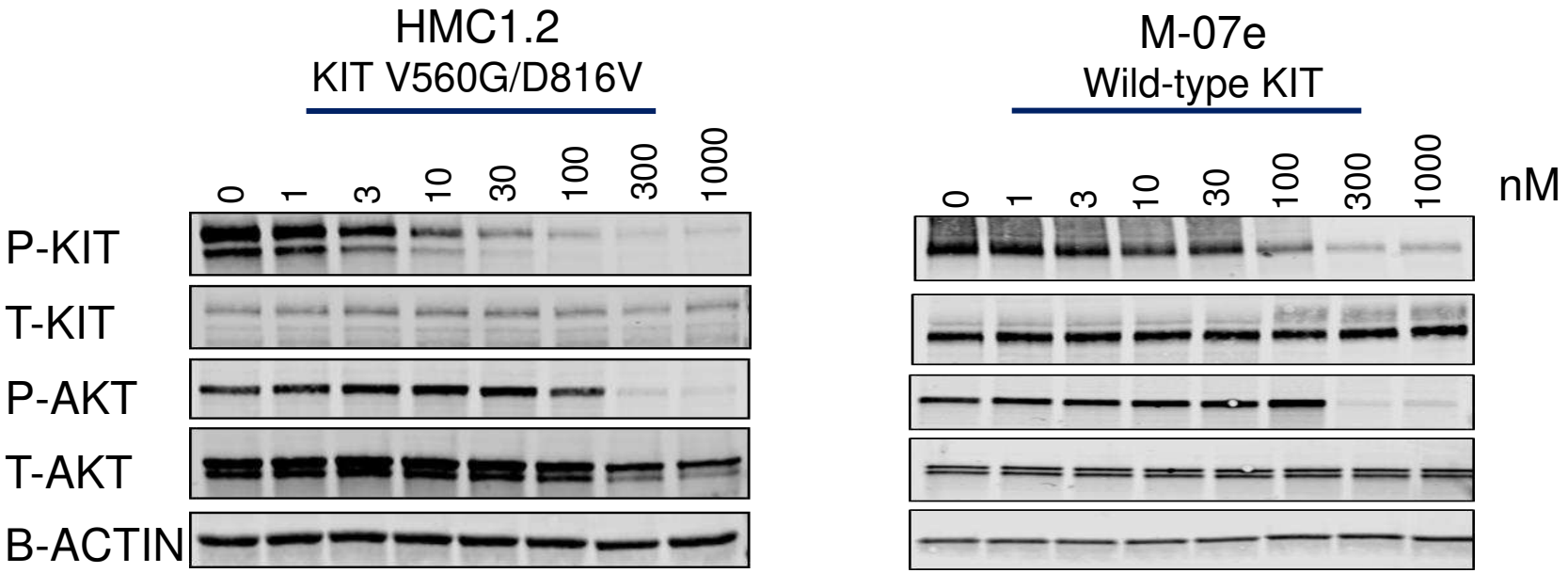


BLU-285 inhibits a broad spectrum of disease relevant KIT mutants more potently than imatinib



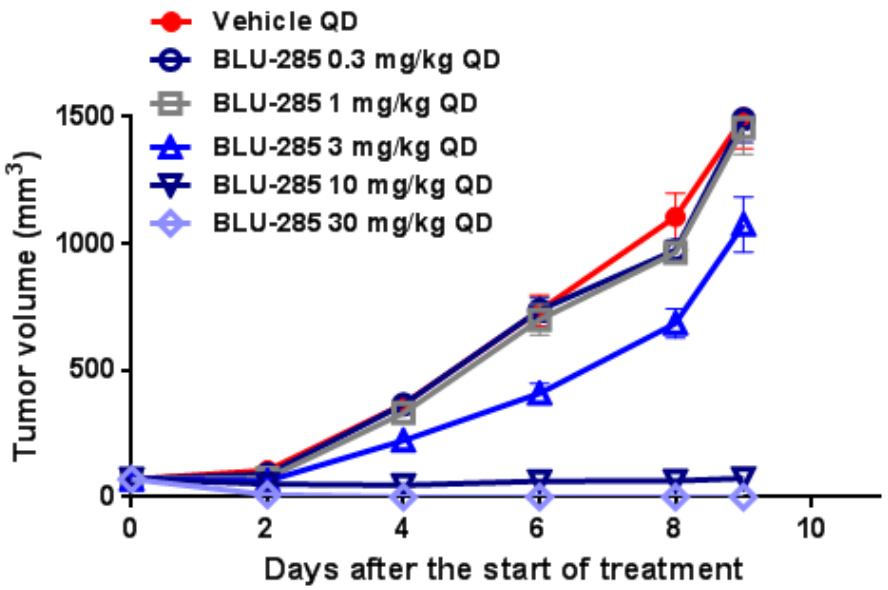
BLU-285 biochemical activity is recapitulated in cells

				P-KIT inhibition	IC_{50} (nM)
Cell Line	KIT mutation	**Exon**	Tissue	**BLU-285**	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	PDGFRα D842V	**18**	engineered	**30**	3145

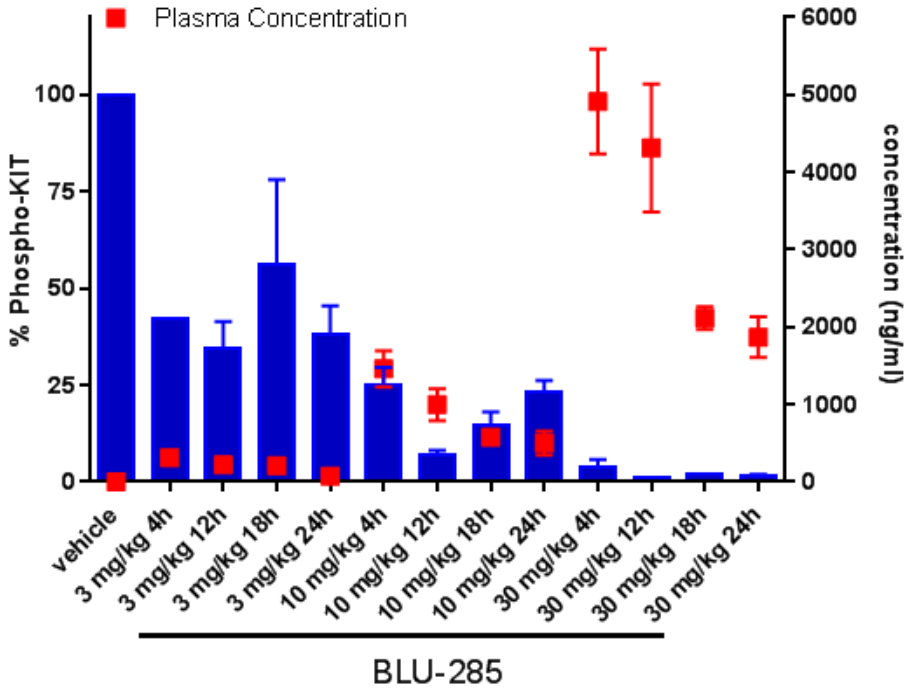


BLU-285 is active in a primary activation loop mutant in vivo model

Tumor Growth



PK-PD

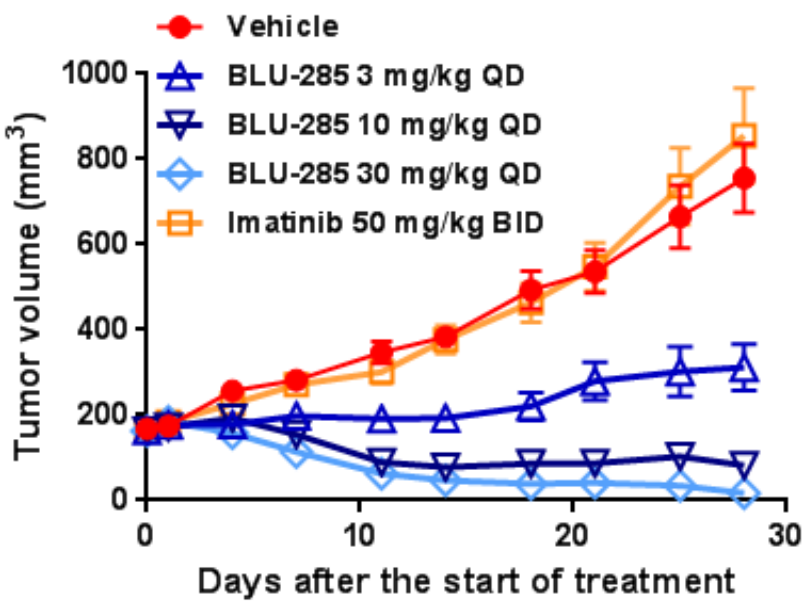


KIT Exon 17-driven P815 mastocytoma allograft:

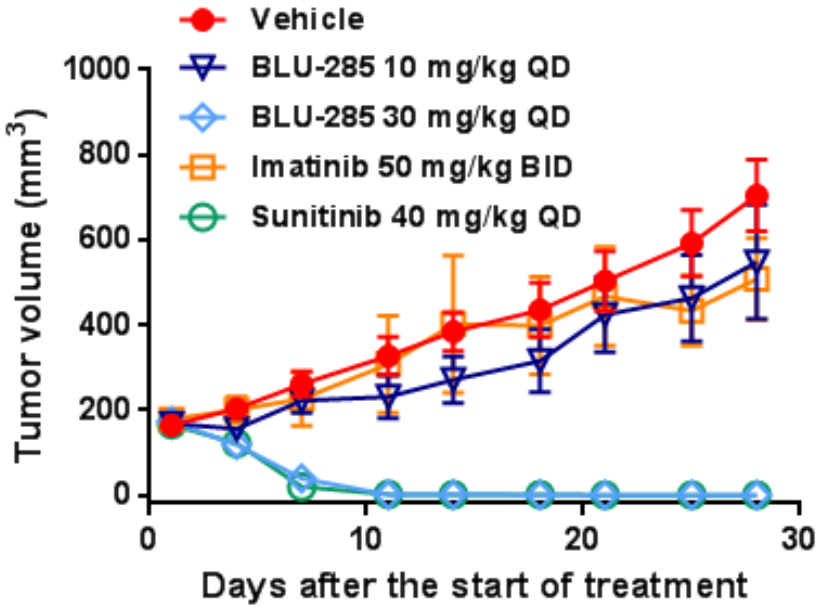
- Mutation in KIT exon 17 equivalent to human **KIT D816Y**
- Tumor regression observed with 10 and 30 mg/kg BLU-285 once daily, oral dosing
- BLU-285 well tolerated at all doses

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

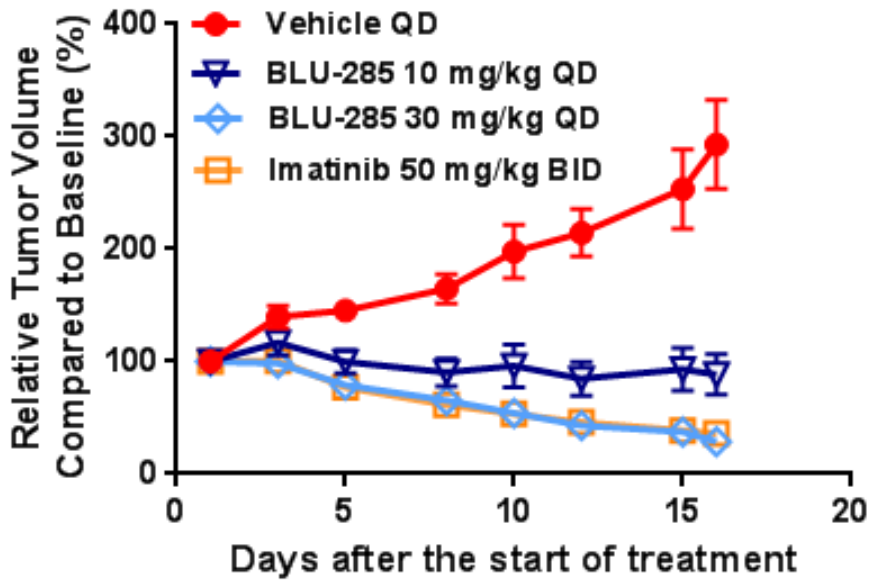


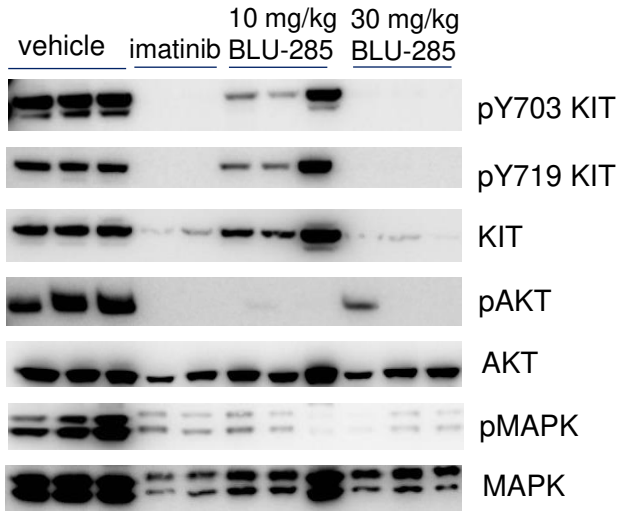
KIT Exon 11/17 mutant (del556-558/Y823D) GIST PDX:
- Tumor regression observed with 10 and 30 mg/kg BLU-285

KIT Exon 11/13 mutant (V559D/V654A) GIST PDX:
- Tumor regression observed with 30 mg/kg BLU-285

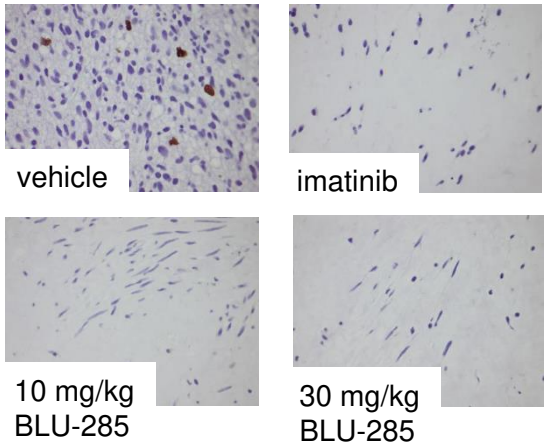
BLU-285 is active in a primary exon 11 mutant GIST PDX model

Tumor Growth
Exon 11 mutant GIST PDX





p-Histone H3 IHC



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

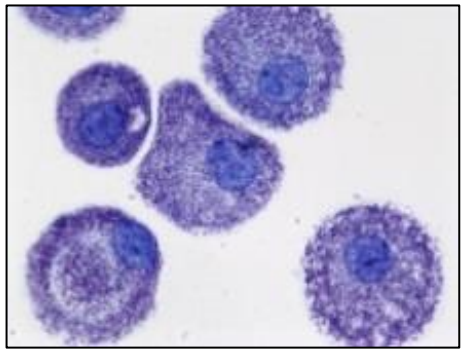
- Collaboration with P. Schoffski, (KU Leuven) Abstract #687 Monday April 3, 1- 5pm.

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

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

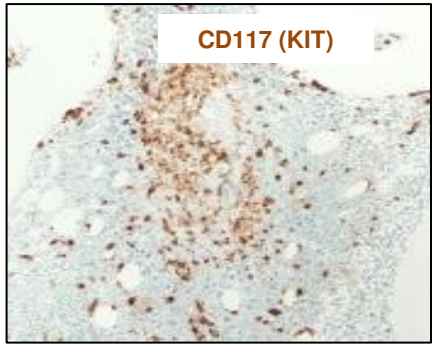
- **Advanced systemic mastocytosis is a rare and severe disease that shortens life expectancy with a wide range of debilitating symptoms and organ damage**

Blood



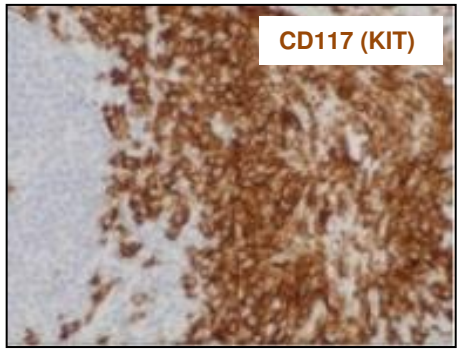
MC degranulation
MC mediator Sx
↑tryptase

Bone and bone marrow



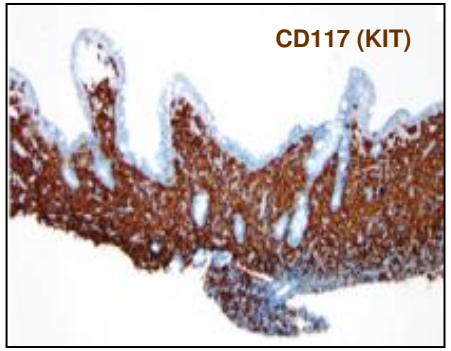
Osteolytic bone lesions
Cytopenias

Liver and Spleen



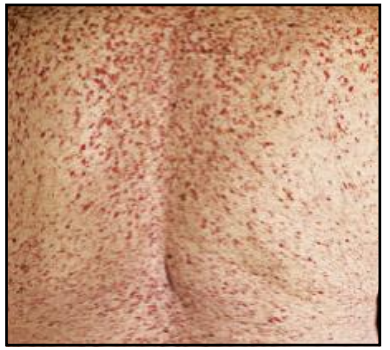
Liver function abnormalities,
Ascites, or Hypersplenism

GI tract



Hypoalbuminemia
Weight loss

Skin



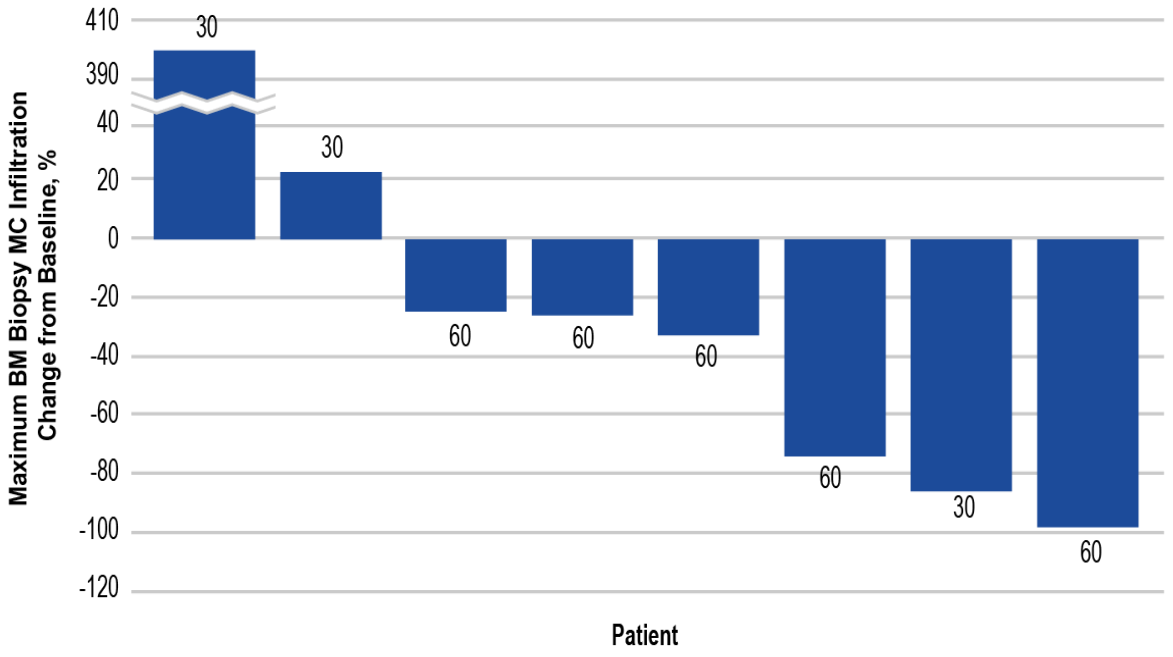
Urticaria
pigmentosa

C-findings

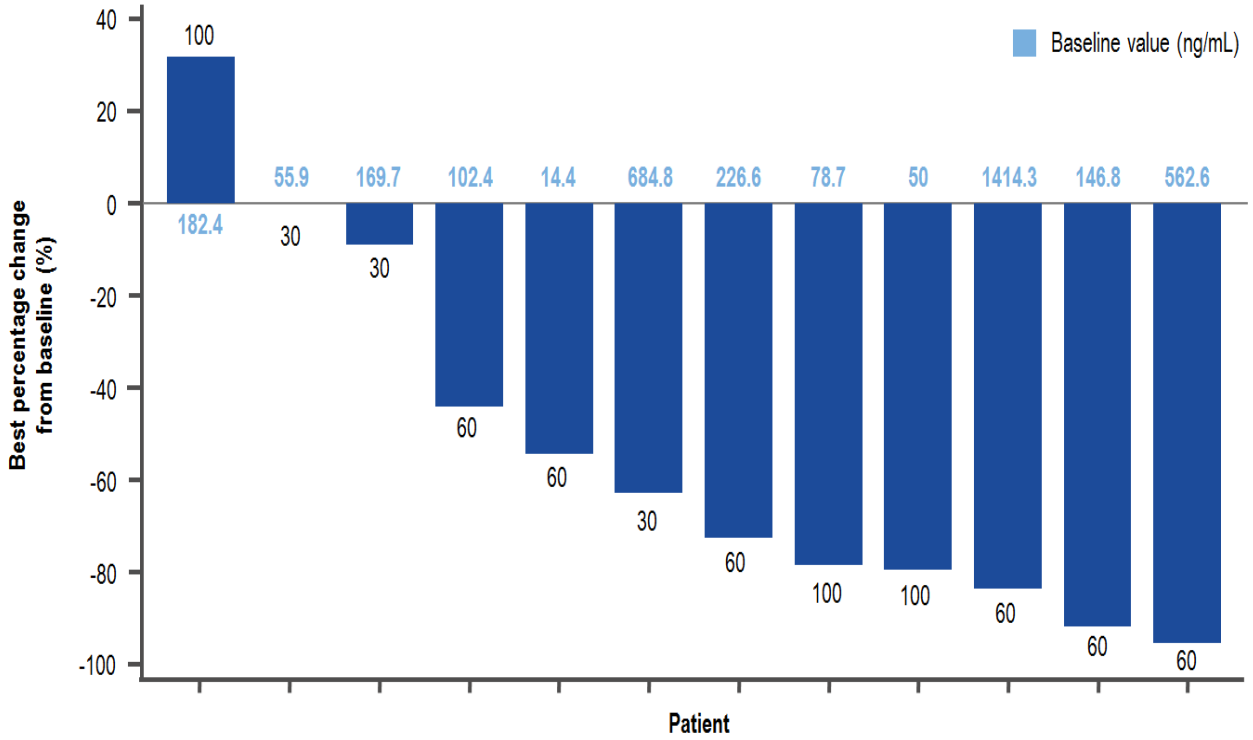
Encouraging clinical activity in phase 1 AdvSM study

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

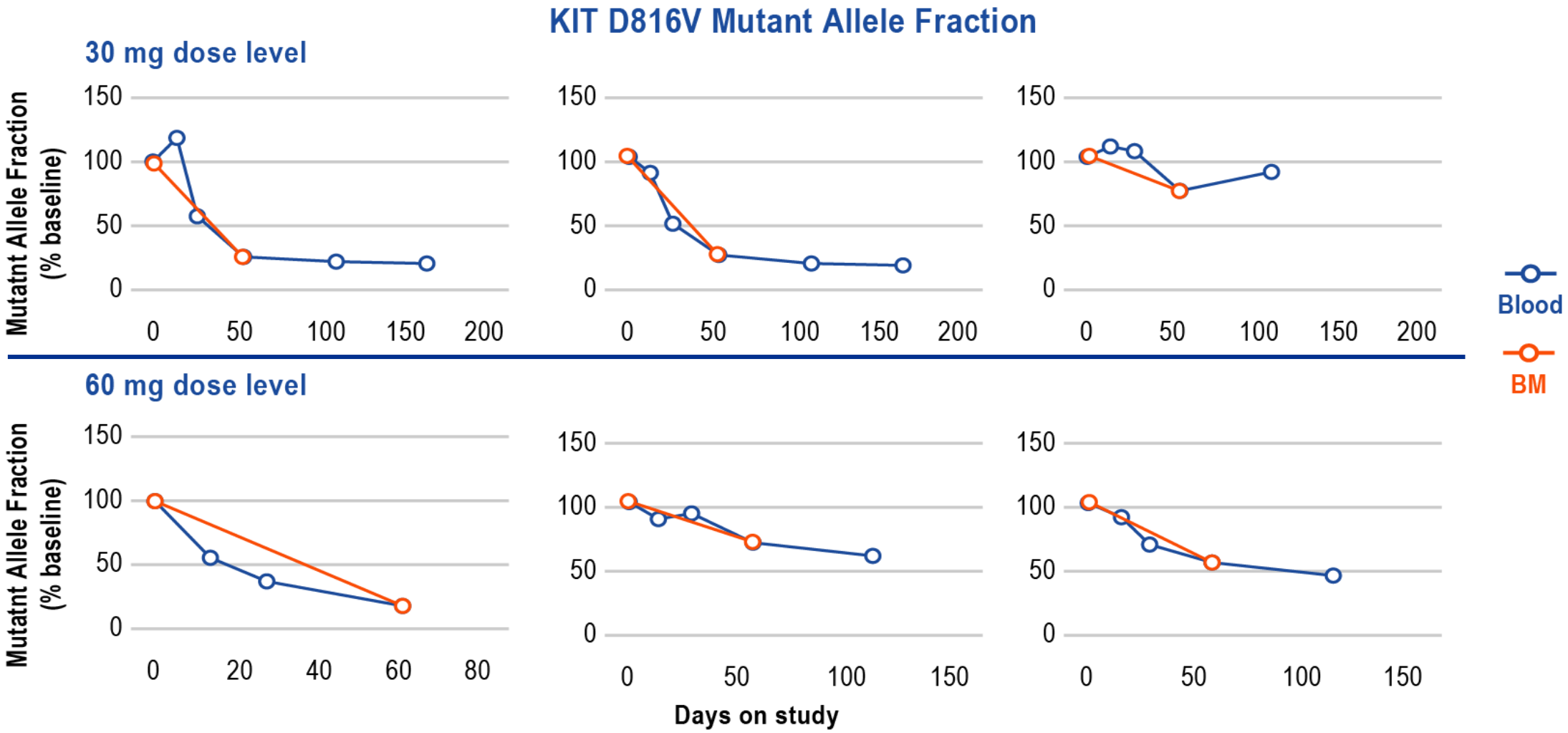


Data cut-off date: November 11, 2016

Drummond et al. 2016 ASH Annual Conference

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

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



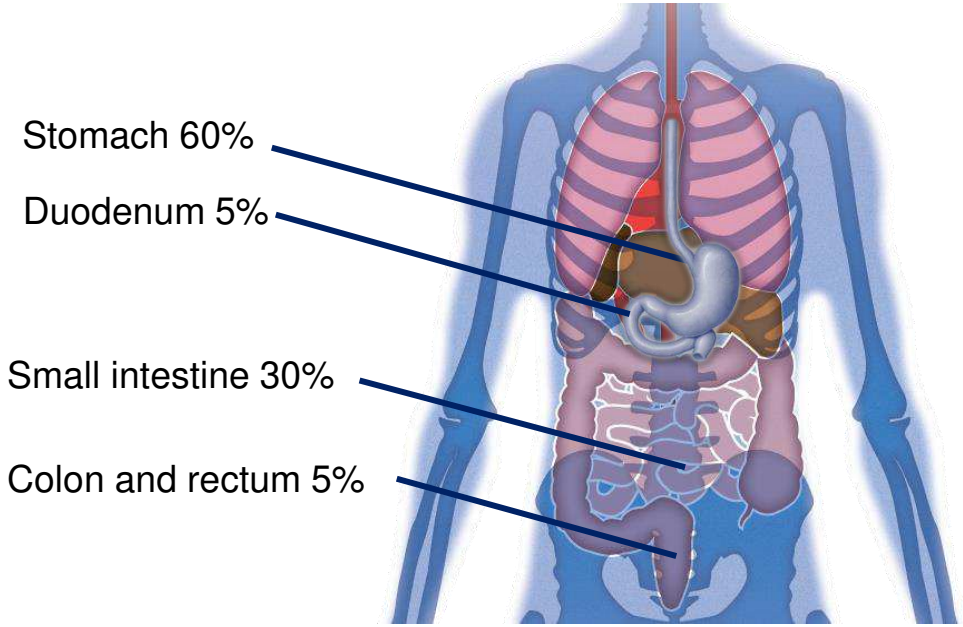
Droplet digital PCR with allele specific primers measures KIT D816V allele burden in blood and BM aspirate

Data cut-off date: November 11, 2016

Drummond et al. 2016 ASH Conference

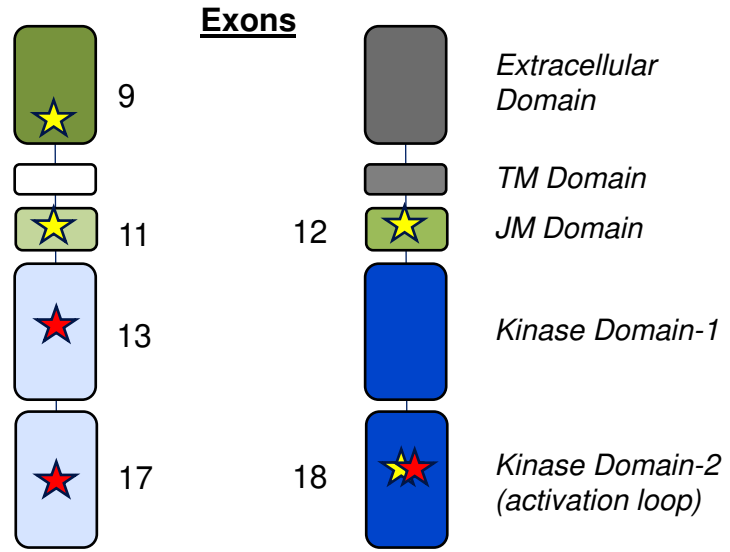
Activating KIT or PDGFRα mutations drive metastatic GIST

Most common GI sarcoma



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

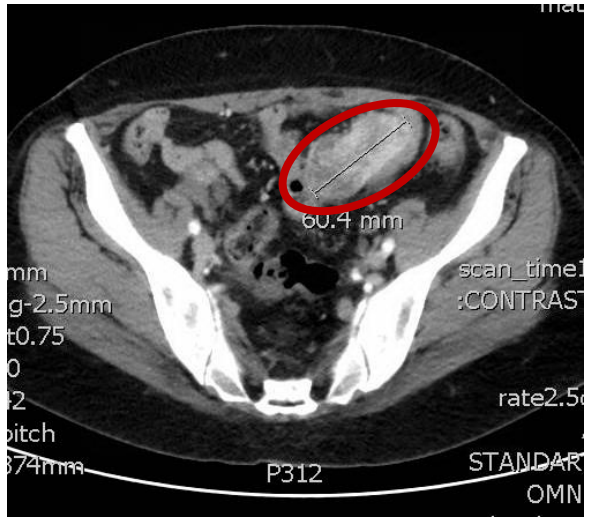
KIT ~ 80% PDGFRα ~ 8%



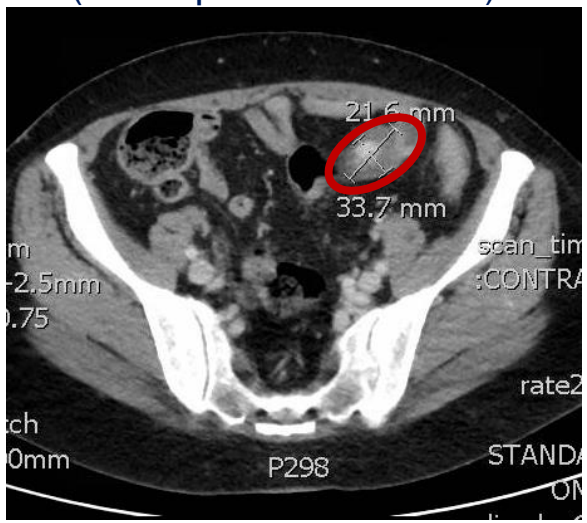
- Primary mutational hotspots ☆
  - KIT Exons 9 or 11
  - PDGFRα Exons 12 and 18 (D842V)
- Resistance mutations ★
  - KIT Exons 13 and 17
  - PDGFRα Exon 18 (D842V)

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

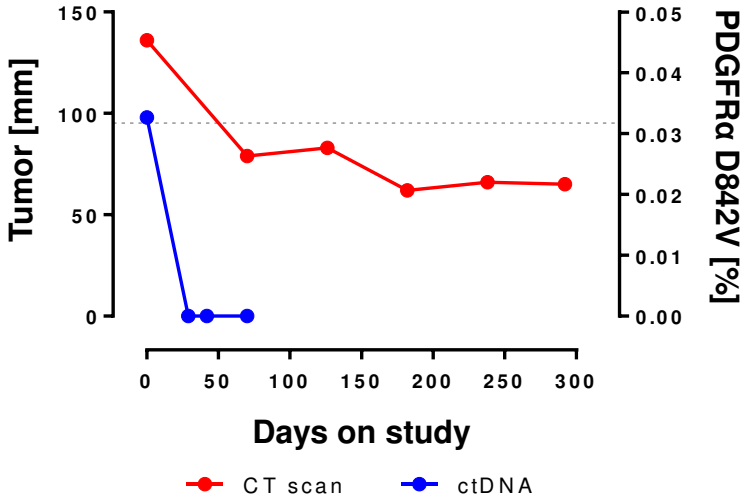
BASELINE



WEEK 8: PARTIAL RESPONSE
(-42% per RECIST1.1)



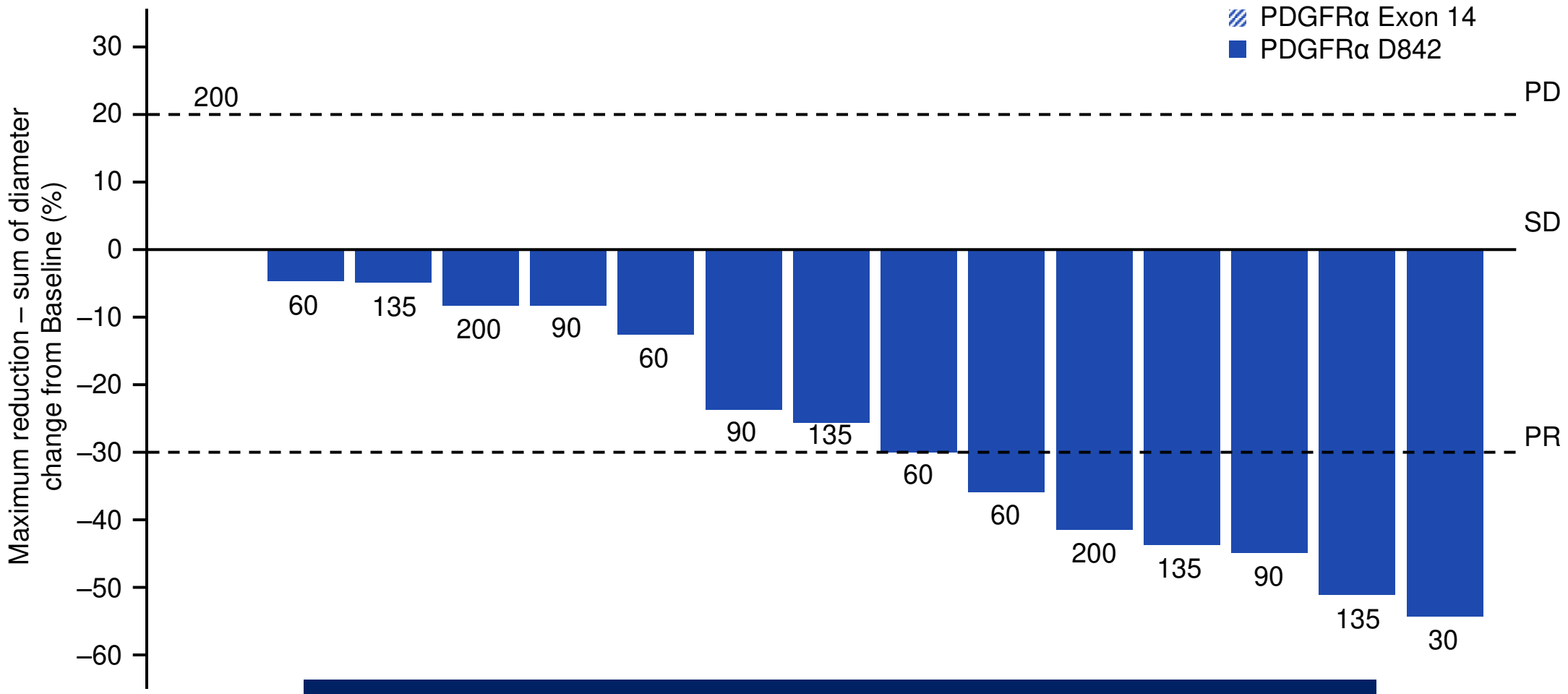
Rapid PDGFRα D842V ct-DNA decline



- *65 year old female, Primary Gastric GIST, PDGFRα 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)

Data cut-off date: November 1, 2016
Heinrich et al. 2016 EORTC-NCI-AACR Conference

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



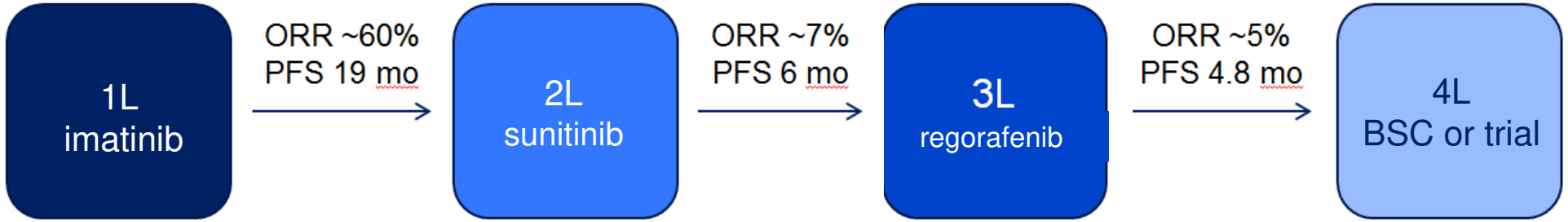
- 14 out of 14 D842-mutant patients with tumor reductions
- ORR = 42%, DCR = 100%

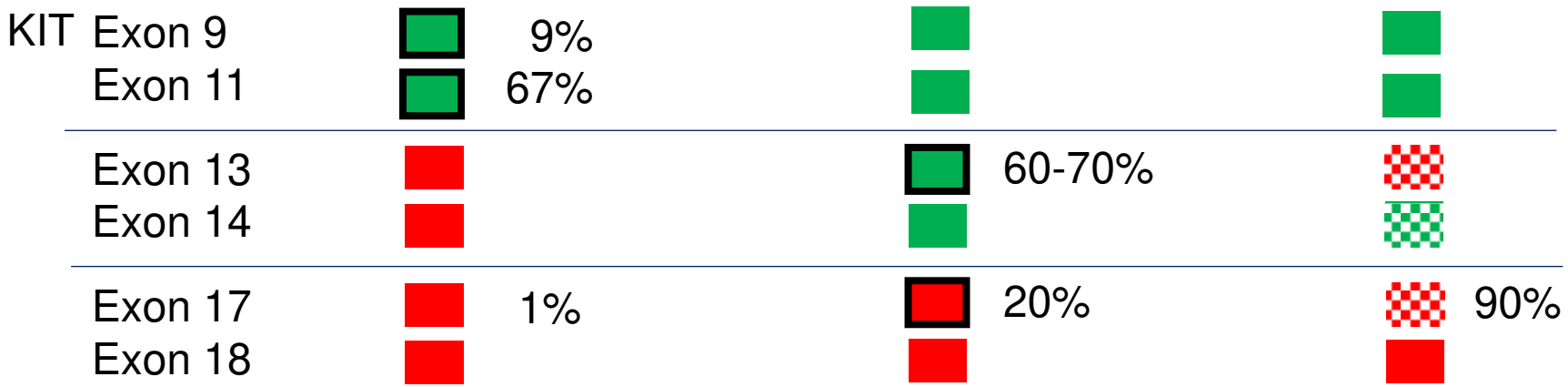
Data cut-off date: November 1, 2016

Heinrich et al. 2016 EORTC-NCI-AACR Conference

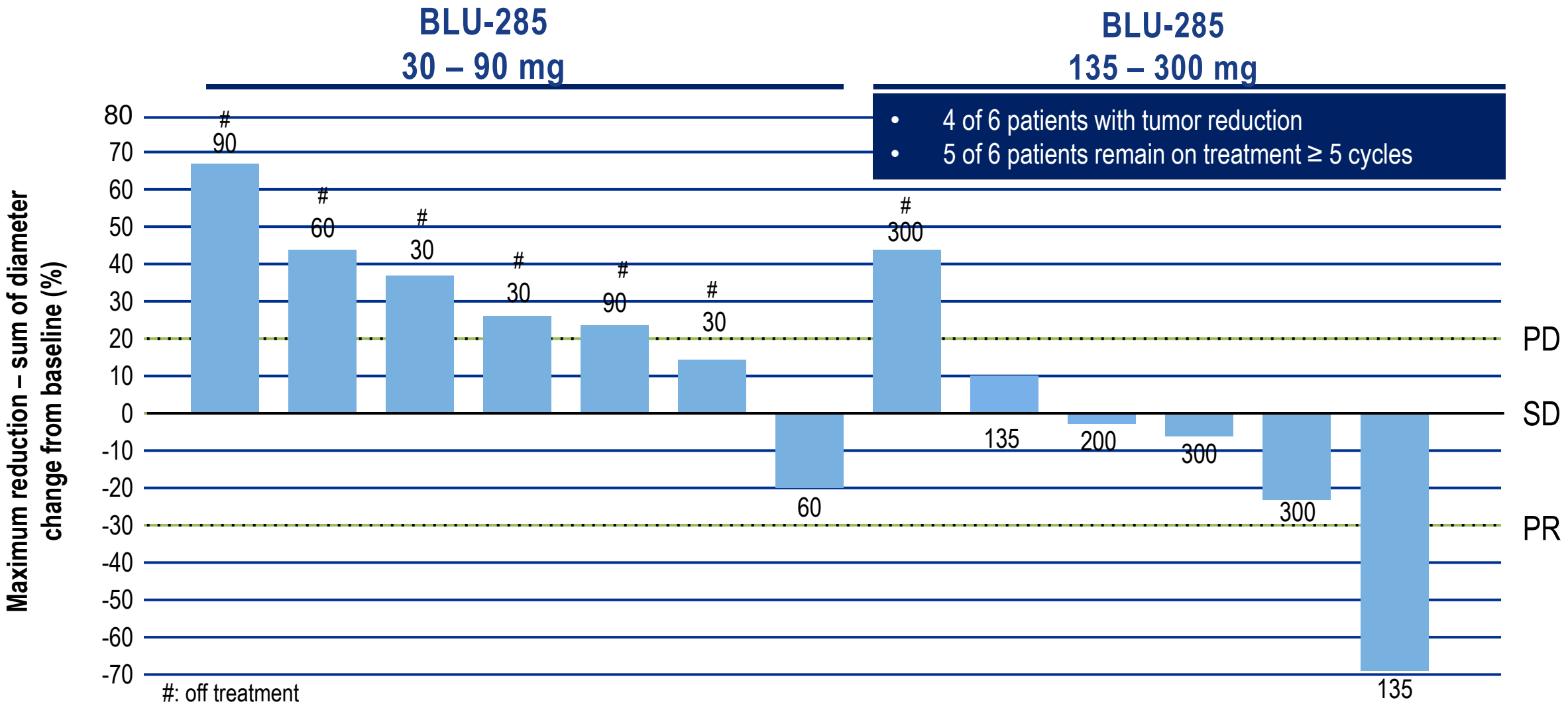
The values above/below the bars denote the dose level (mg) QD received by each patient

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





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

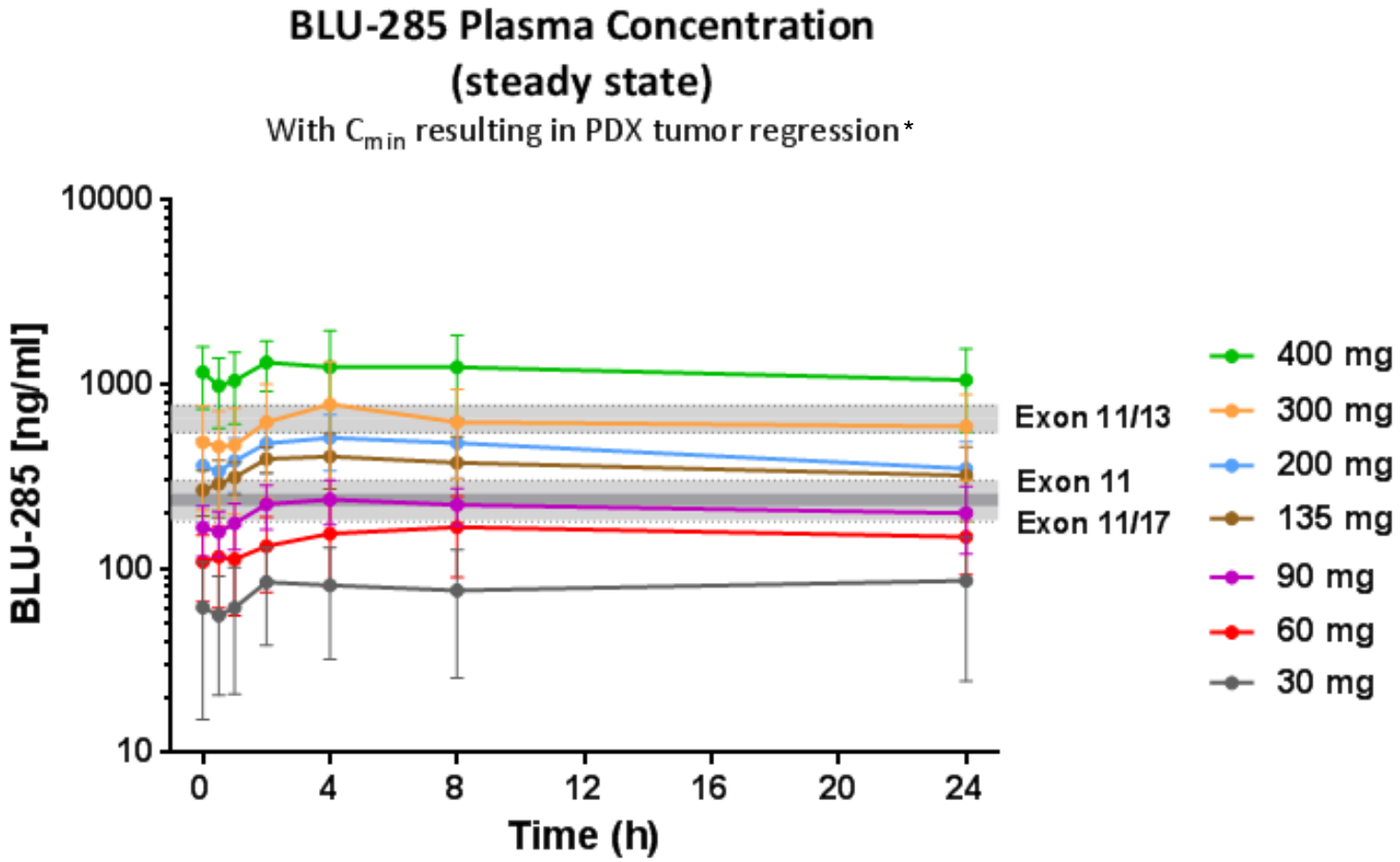


Data cut-off date: November 1, 2016
Heinrich et al. 2016 EORTC-NCI-AACR Conference

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

BLU-285 demonstrates dose dependent human pharmacokinetics

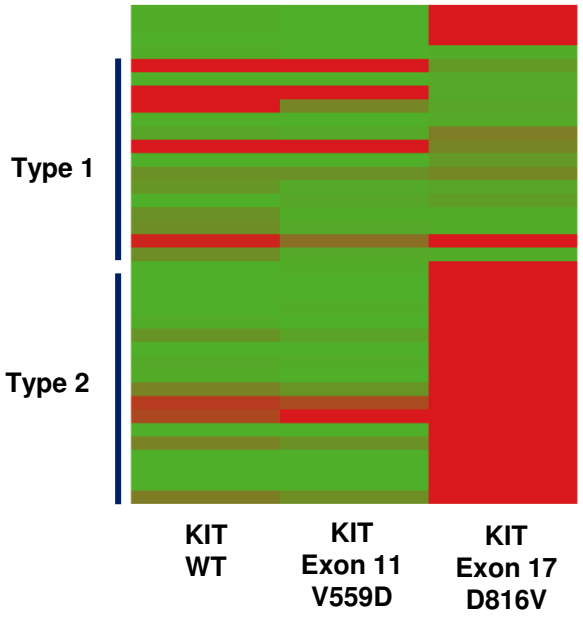
PDX studies suggest clinical exposures in therapeutic range



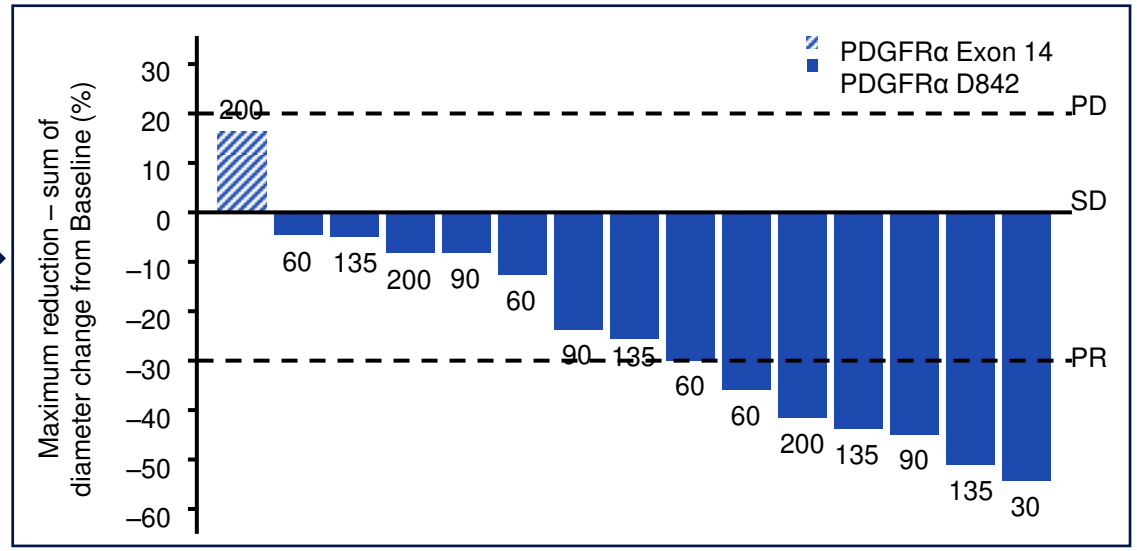
- PDX data suggest active dose range for KIT mutant GIST at levels ≥ 135 mg
- Expansion cohorts for GIST phase 1 trial recently initiated with RP2D of 400 mg QD

*Exposures adjusted for free fraction

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



[chemical structure for BLU-285 removed]



- KIT/PDGFRα activation loop mutants are unaddressed by approved therapies
- Insights from BPMC 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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