Preliminary safety and activity in a first-in-human Phase 1 study of BLU-285, a potent, highly selective inhibitor of KIT and PDGFRα activation loop mutants in advanced gastrointestinal stromal tumor (GIST)

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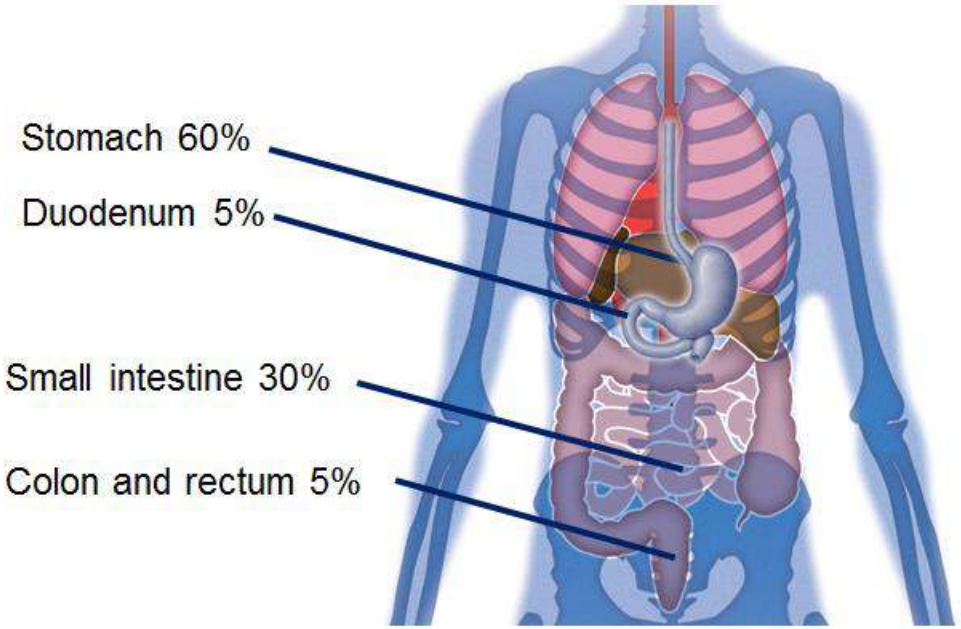
Disclosures

- BLU-285 is an investigational agent currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
- Dr. Michael Heinrich is an investigator for Blueprint Medicines' ongoing Phase 1 study in unresectable gastrointestinal stromal tumor
- Dr. Michael Heinrich has the following disclosures:
  - Consultant: Blueprint Medicines, Novartis, MolecularMD
  - Equity interest: MolecularMD
  - Research funding: Blueprint Medicines, Deciphera, Ariad
  - Expert testimony: Novartis
  - Patents: four patents on diagnosis and treatment of PDGFRα-mutant GIST

Gastrointestinal Stromal Tumor (GIST)

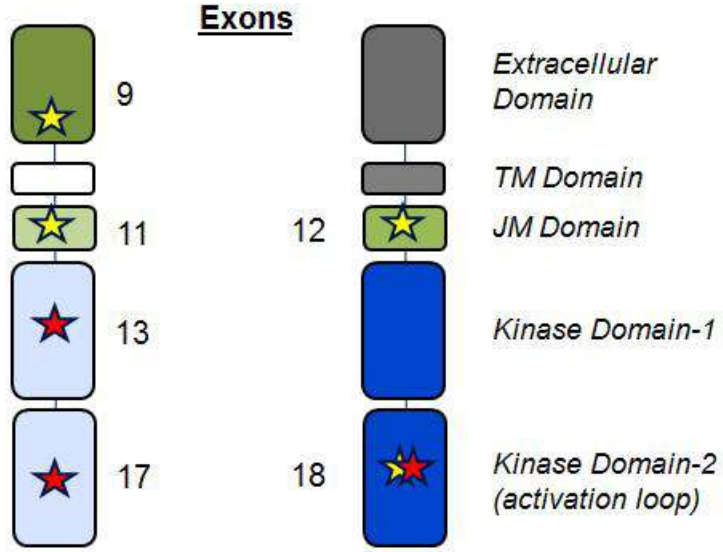
Most common GI sarcoma



- Cancer of the interstitial cells of Cajal
- Primary tumor usually presents as a stomach or intestinal mass
- Metastatic recurrences spread to liver, peritoneum, and other distant sites
- Chemotherapy has no impact

Activating RTK mutations drive metastatic GIST

KIT ~ 80% **PDGFRα ~ 8%**

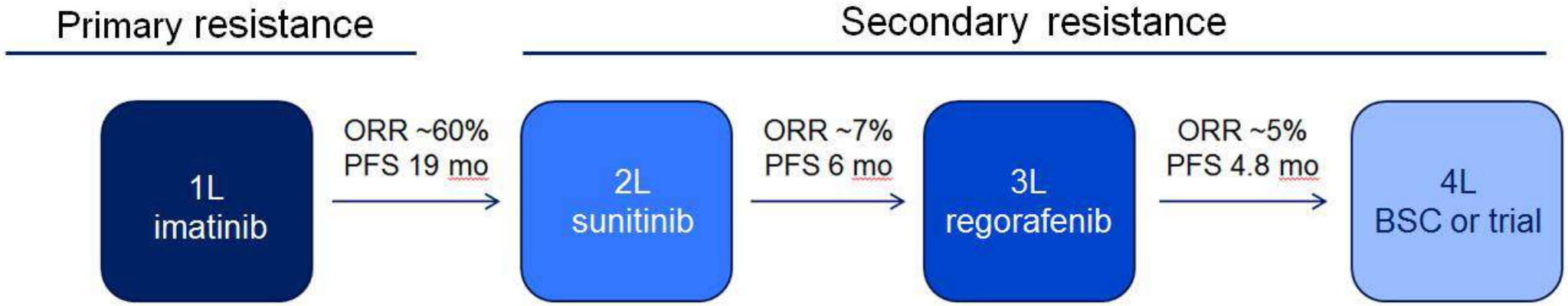


- Primary mutational hotspots ☆
  - KIT Exons 9 or 11
  - PDGFRα D842V Exons 12 and 18
- Resistance mutations ★
  - KIT Exons 13 and 17
  - PDGFRα D842V Exon 18

GI, gastrointestinal; JM, juxtamembrane; KIT, receptor tyrosine kinase protein; PDGFRα, platelet-derived growth factor receptor; RTK, receptor tyrosine kinase; TM, transmembrane

Barnett & Heinrich (2012) Am Soc Clin Oncol Educ Book;663; Nowain et al (2005) J Gastroen Heptol;20:818; Dematteo et al (2000) Ann Surg;231:51; Plumb et al (2013) Clin Radiol;68:770; Joensuu (2006) 17 Suppl 10:x280

Advanced GIST has high medical need



	Prevalence	
Resistance mutation	**Primary**	**Secondary**
KIT Exon 17	~ 1%	2L ~ 20% 3L ~ 90%
PDGFRα D842V	~ 5-6%	rare

- Activation loop mutations are associated with resistance to therapy
- Approved agents are ineffective against PDGFRα D842V
  - ORR ~ 0%
  - mPFS ~ 3 months

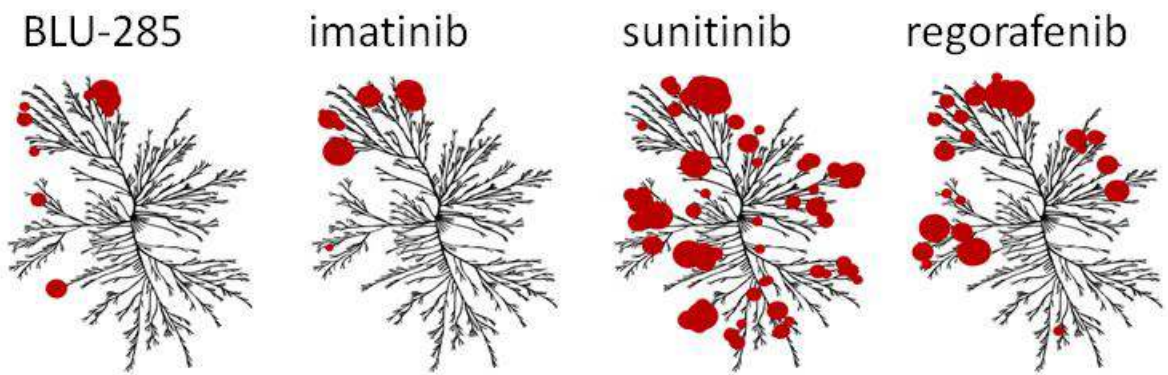
mPFS, median progression-free survival; ORR, objective response rate; PFS, progression-free survival

Cassier (2012) CCR;*18:4458*; Yoo (2016) Can Res Treat;48:546; Corless (2005) JCO;*23:5357*; Barnett and Heinrich (2012) Am Soc Clin Onc Ed Book: 663; Demetri (2006) Lancet;*368:1329*; Demetri (2013) Lancet;*381:295-302*

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

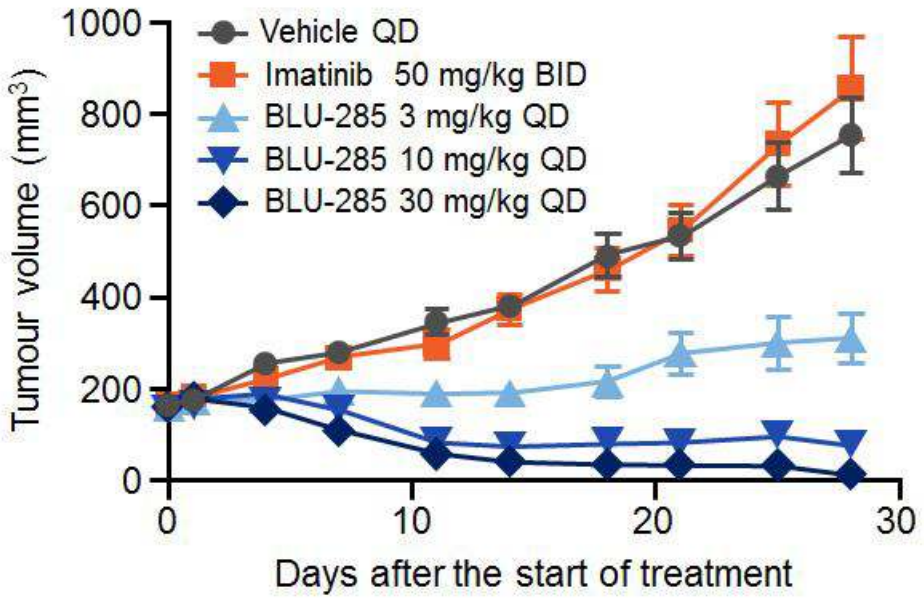
Biochemical profiles

	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
sunitinib	120	207	97.2
regorafenib	810	3640	1685



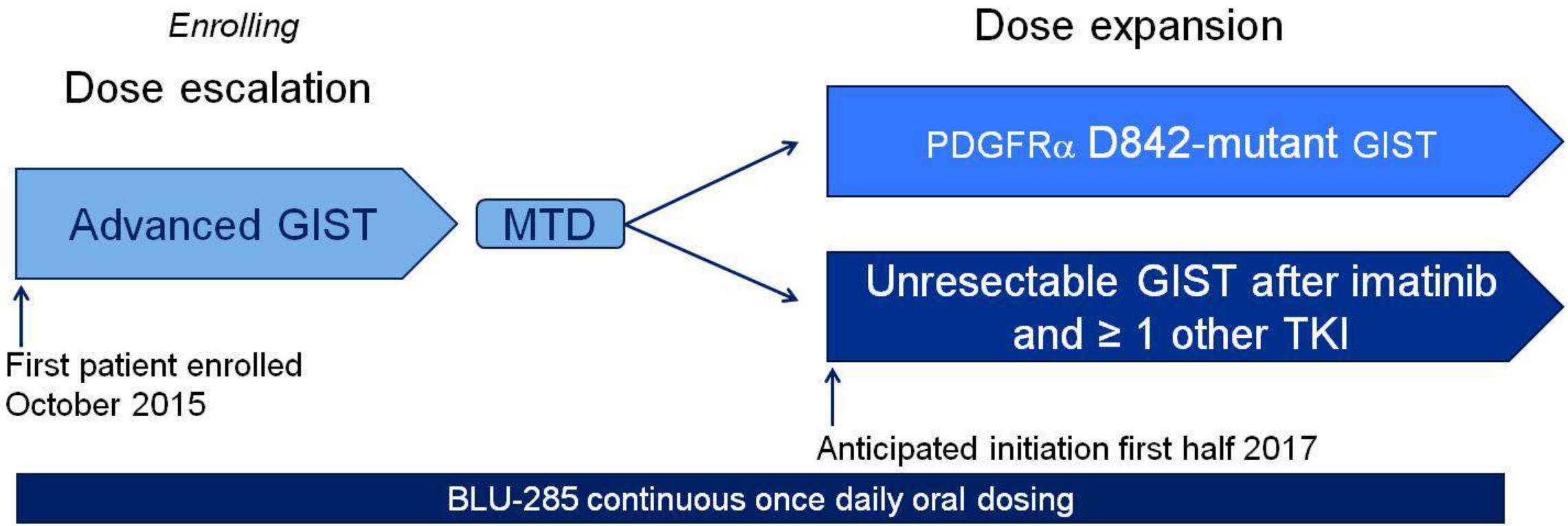
BID, twice daily; IC_{50}, half maximal inhibitory concentration; PDX, patient derived xenograft; QD, once daily
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

Tumor regression in KIT exon 11/17* mutant GIST PDX



*del556-558/Y823D

BLU-285 Phase 1 study



- Primary objectives – determine the MTD and RP2D, and assess safety and tolerability
- Secondary objectives – PK, mutational status, anti-tumor activity

MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended Phase 2 dose; TKI, tyrosine-kinase inhibitor
NCT02508532

Demography and baseline patient characteristics

Parameter	All patients, N = 36
Age (years), median (range)	61 (41 – 77)
	n (%)
GIST subtype	
KIT mutant	18 (50)
PDGFRα mutant	18 (50)
Metastatic Disease	35 (97)
Largest target lesion size (cm)	
≤ 5	8 (22)
> 5 – ≤ 10	12 (33)
> 10	14 (39)
pending	2 (6)
#Prior TKI, median (range)	3.5 (0 – 12)
≤ 2	12 (33)
> 2	24 (67)

Data are preliminary and based on a cut off date of 1 November 2016

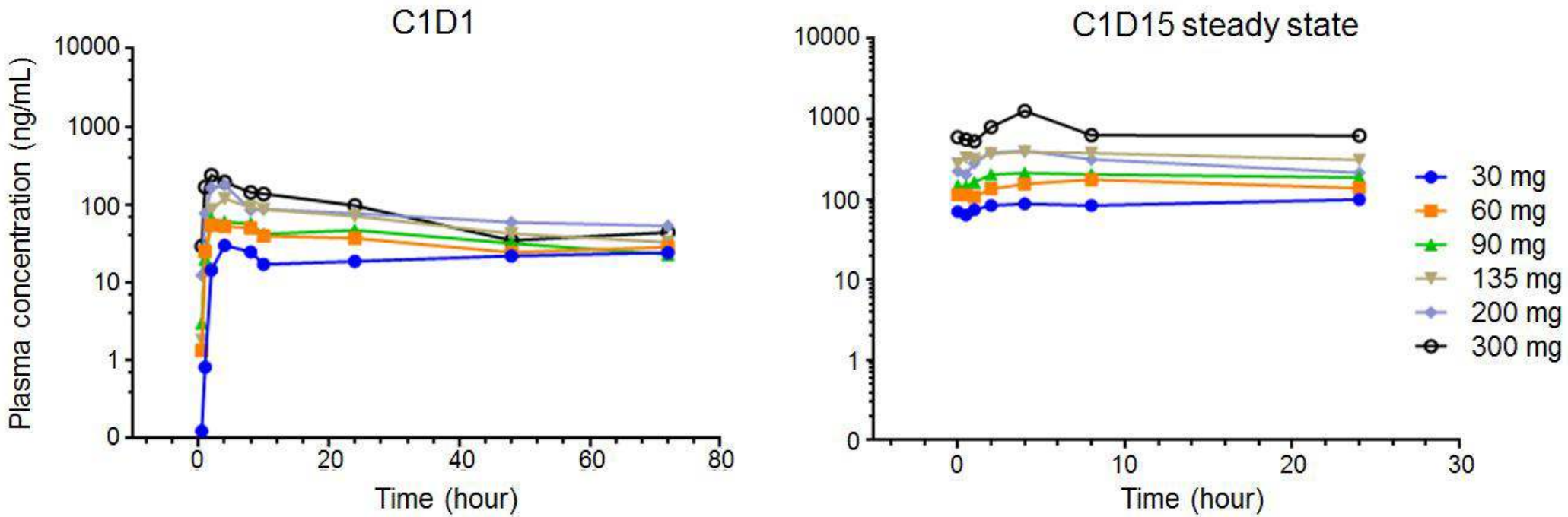
Initial dose escalation results

- Patients with unresectable GIST
  - Prior imatinib and ≥ 1 TKI
  - PDGFRα D842 mutation regardless of prior therapy
- 3 + 3 dose escalation with additional accrual to dose levels declared safe at a dose escalation meeting
- 36 patients enrolled over 12 months
- MTD has not been reached

BLU-285 mg/day	Patients treated by dose N = 36
30	3 + 2 enrichment
60	3 + 3 enrichment
90	3 + 3 enrichment
135	3 + 3 enrichment
200	3 + 2 enrichment
300	3 + 1 enrichment
400	4

- 75% (n=27) of patients remain on treatment, range 0.8 – 12.3 months
- All PDGFRα patients remain on treatment
- 9 patients off treatment (all due to progressive disease)

BLU-285 pharmacokinetics support once daily dosing

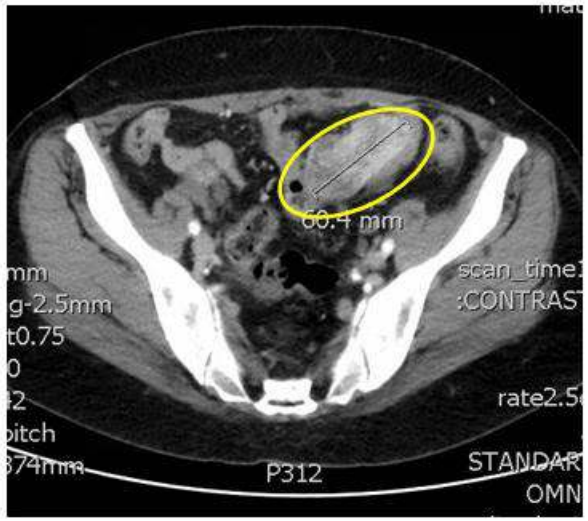


- Half-life > 24 hour, supporting QD dosing
- Relatively rapid absorption: T_{max} ~ 2 – 8 hr
- Accumulation in plasma: 2.5 – 4.7 -fold after 15 days
- Exposure at 300 mg is at low end of predicted therapeutic range based on KIT Exon 17 mutant xenograft studies

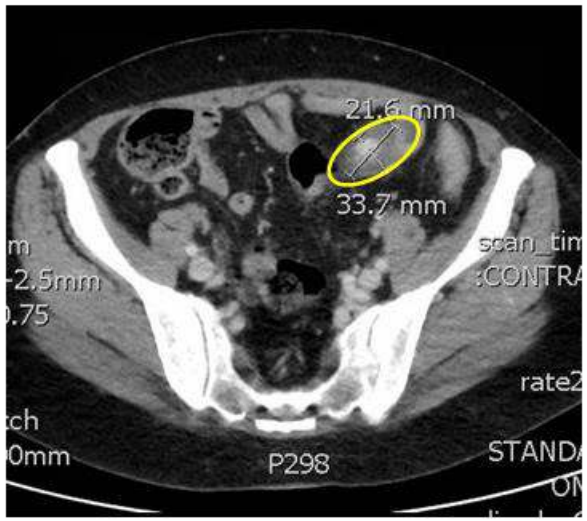
C1D1, Cycle 1 Day 1; C1D15, Cycle 1 Day 15; T_{max}, time at which C_{max} is observed; QD, once daily

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

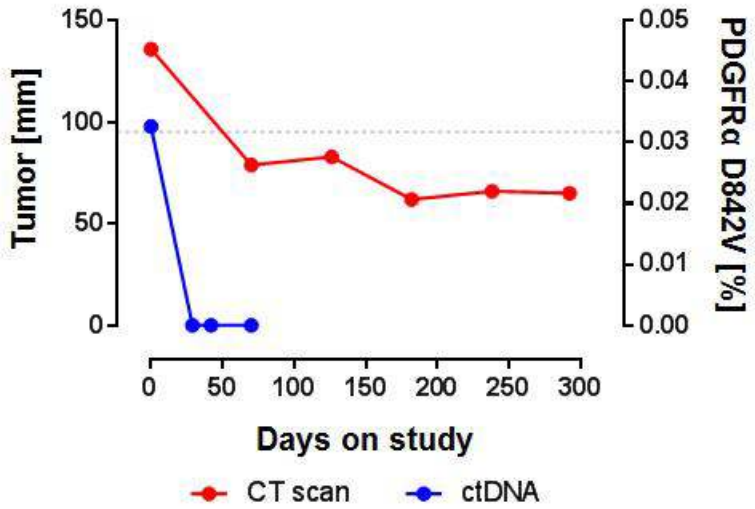
Baseline



After 8 weeks, partial response (-42%)



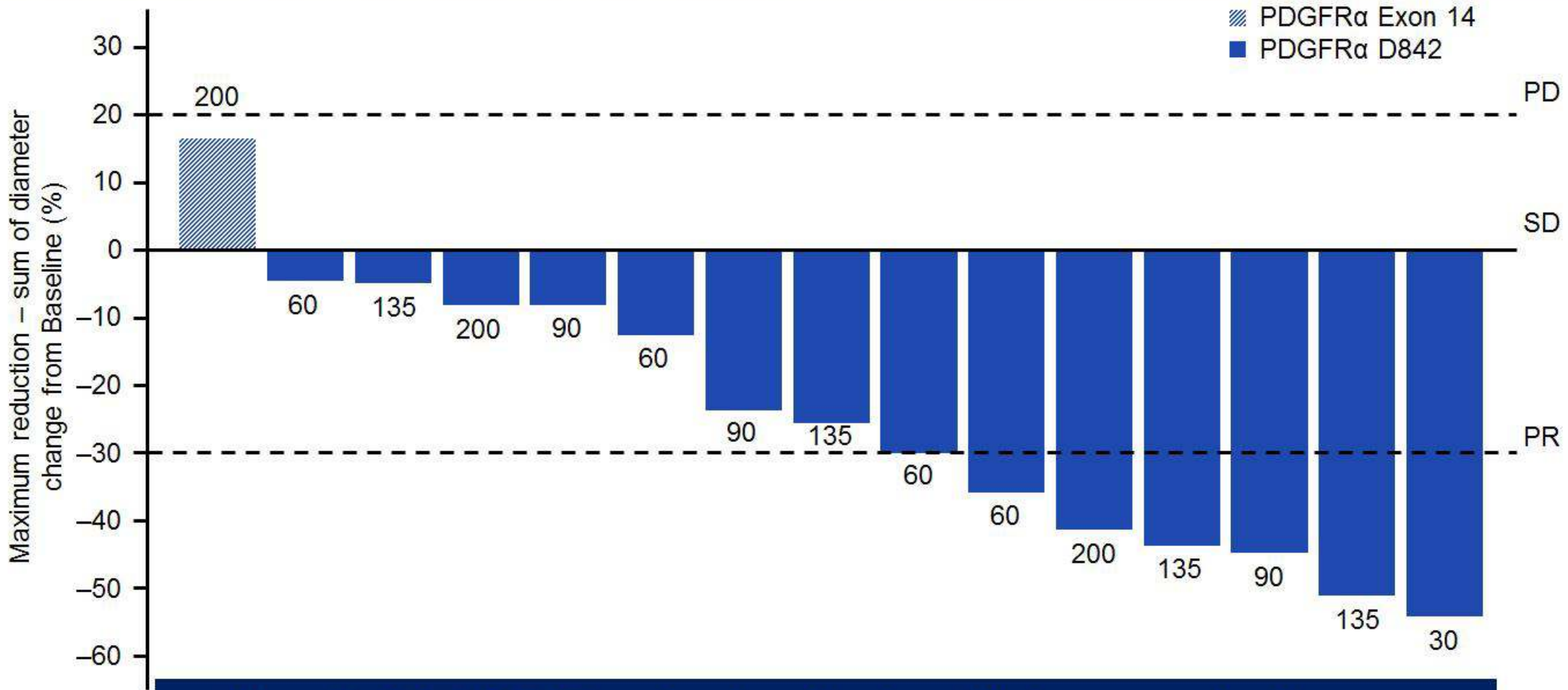
Rapid PDGFRα D842V ct-DNA decline



- *65 yo 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 RECIST 1.1)

CT, computerized tomography; ct-DNA, circulating tumor DNA; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors

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

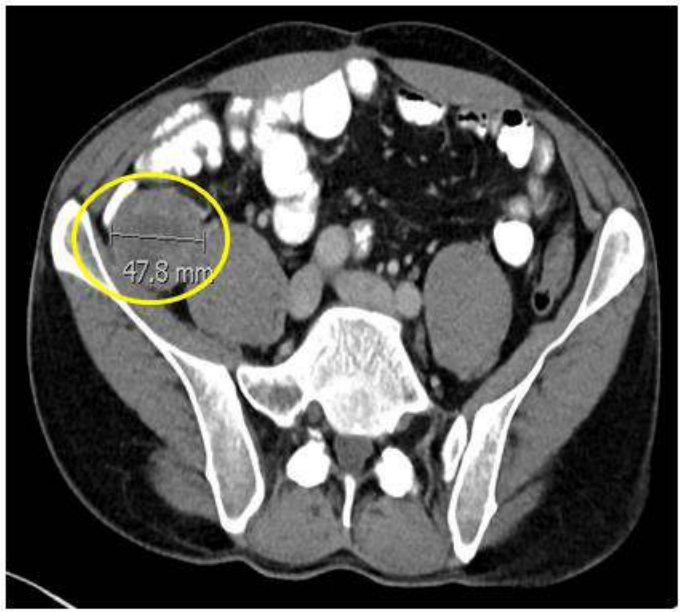


- 14 out of 14 D842-mutant patients with tumor reductions
- All PDGFRα patients remain on treatment

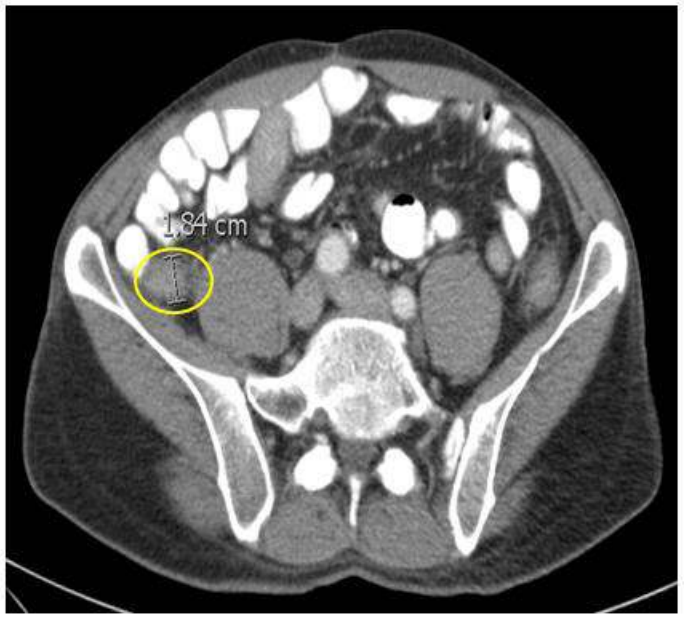
The values above/below the bars denote the dose level (mg) QD received by each patient
SD, stable disease; PD, progressive disease; PR, partial response

Radiographic response per RECIST 1.1 in heavily pretreated KIT Exon 11/17 GIST (dose level 4, 135 mg)

Baseline

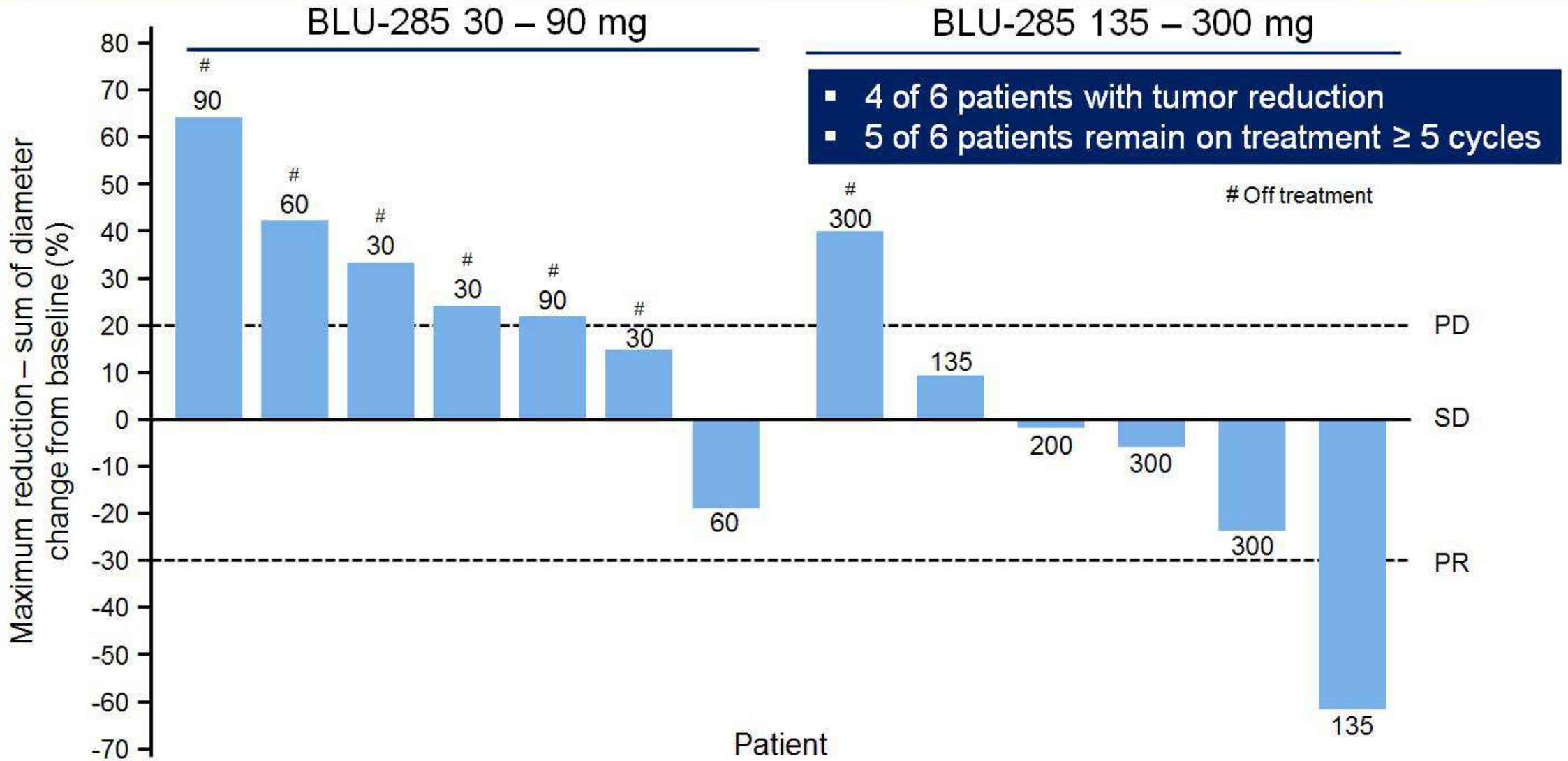


After 24 weeks,
partial response (-62%)



- 57 year old male, KIT Exon 11 (delWK557-8)/Exon 17 (D816V) mutations
  - Prior imatinib, sunitinib, nilotinib, sorafenib, imatinib + BKM120
  - Ongoing at Cycle 8 with confirmed partial response per RECIST 1.1

KIT GIST - early dose-response relationship



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

Best radiographic response with BLU-285 per RECIST 1.1

Best response (per investigator)	PDGFRα N=15 n (%)	KIT N=13 n (%)	Total N=28 n (%)
PR	6 (40)	1 (8)	7 (25)
SD	9 (60)	6 (46)	15 (54)
DCR (PR +SD)	15 (100)	7 (54)	22 (79)
PD	0	6 (46)	6 (21)

- Of 7 partial responses, 6 confirmed; 1 pending (still on treatment)

DCR, disease control rate

Adverse events associated with BLU-285

- No DLTs or treatment-related Grade 4 – 5 AEs
- No patient discontinued BLU-285 due to treatment-related toxicity
- 11 (31%) patients had Grade 3 or higher AEs; of these, 3 were considered treatment-related:
  - 1 patient with Grade 3 nausea and vomiting
  - 1 patient with Grade 3 anemia and intratumoral hemorrhage
  - 1 patient with Grade 3 hypophosphatemia
- AEs occurring in ≥ 20% of patients
  - Nausea (42%)
  - Vomiting (33%)
  - Peripheral edema (31%)
  - Fatigue (28%)
  - Constipation (22%)

AE, adverse event; DLT, dose limiting toxicity

Summary

- BLU-285 has been well tolerated on a QD schedule at doses of 30 – 400 mg
- Half-life > 24 hours, supports QD dosing
- BLU-285 demonstrates strong clinical activity in PDGFRα D842-mutant GIST at all dose levels
- Significant anti-tumor activity in TKI-resistant, KIT-mutant GIST observed at doses ≥ 135 mg with tumor reduction in 4 of 6 patients, including 1 PR
- Dose escalation continues with the goal of maximizing clinical activity in KIT-mutant GIST and to define the MTD and RP2D
- Anticipate initiation of expansion cohorts in first half of 2017

Acknowledgments

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