GIST: imatinib and beyond

Clinical activity of BLU-285 in advanced gastrointestinal stromal tumor (GIST)

Michael Heinrich[1], Robin Jones[2], Margaret von Mehren[3], Patrick Schoffski[4], Sebastian Bauer[5], Olivier Mir[6], Philippe Cassier[7], Ferry Eskens[8], Hongliang Shi[9], Terri Alvarez-Diez[9], Oleg Schmidt-Kittler[9], Mary Ellen Healy[9], Beni Wolf[9], Suzanne George[10]

[1]Oregon Health & Sciences University, Oregon, USA; [2]Royal Marsden Hospital/Institute of Cancer Research, London, UK; [3]Fox Chase Cancer Center, Pennsylvania, USA; [4]Leuven Cancer Institute, Leuven, Belgium; [5]University of Essen, Essen, Germany; [6]Institut Gustave Roussy, Paris, France; [7]Centre Leon Berard, Lyon, France; [8] Erasmus MC Cancer Institute, Rotterdam, Netherlands; [9]Blueprint Medicines Corporation, Massachusetts, USA; [10]Dana-Farber Cancer Institute, Massachusetts, USA

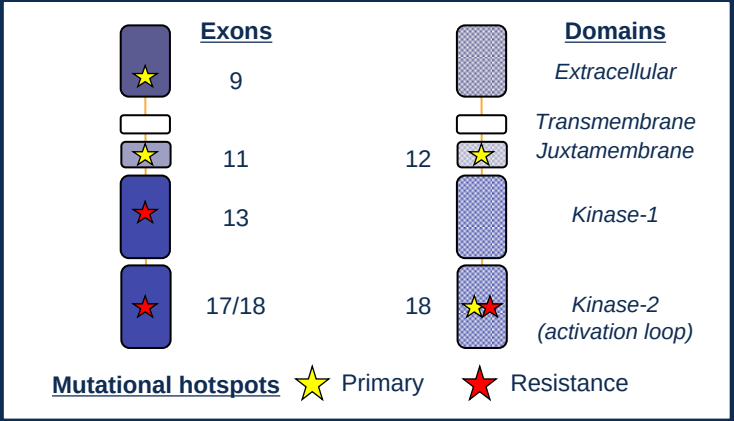
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Abstract no: 11011 Presented by: Dr. Michael Heinrich

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 studies 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

Imatinib revolutionized Gastrointestinal Stromal Tumor (GIST) treatment

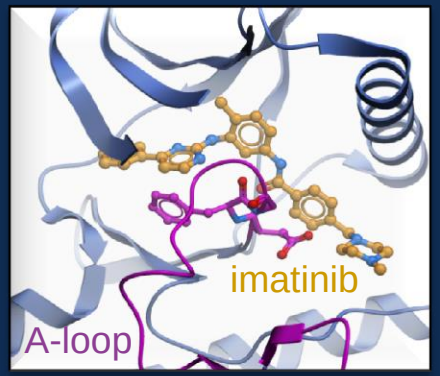
KIT PDGFRα



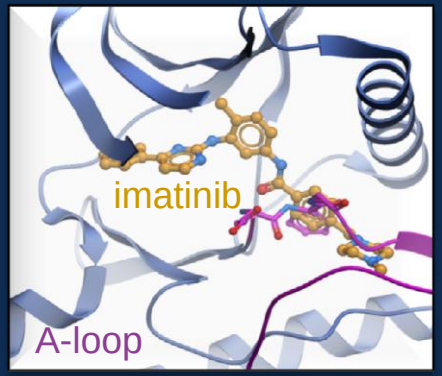
- KIT mutations drive ~75–80% of GIST
- PDGFRα mutations drive ~5–10% of GIST

KIT

Inactive conformation

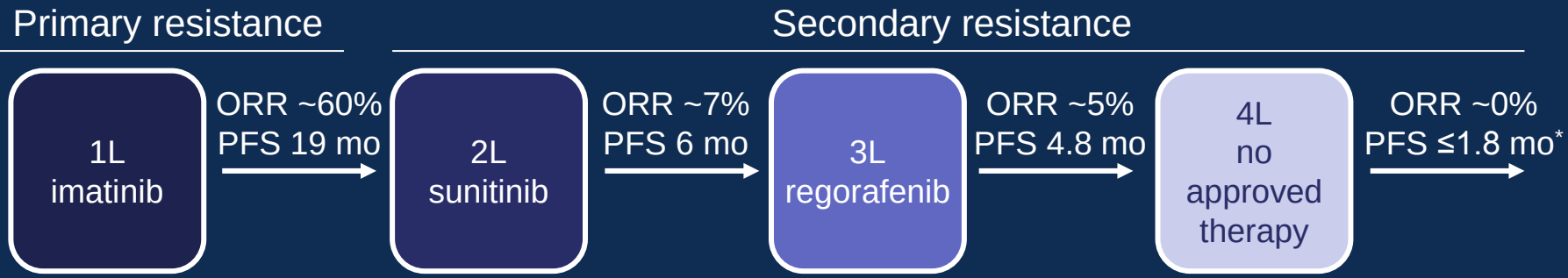


Active conformation



- Imatinib binds the inactive kinase conformation and inhibits many primary mutants
- Imatinib is a highly effective first-line GIST therapy

Beyond imatinib, there are no highly effective therapies[1–6]

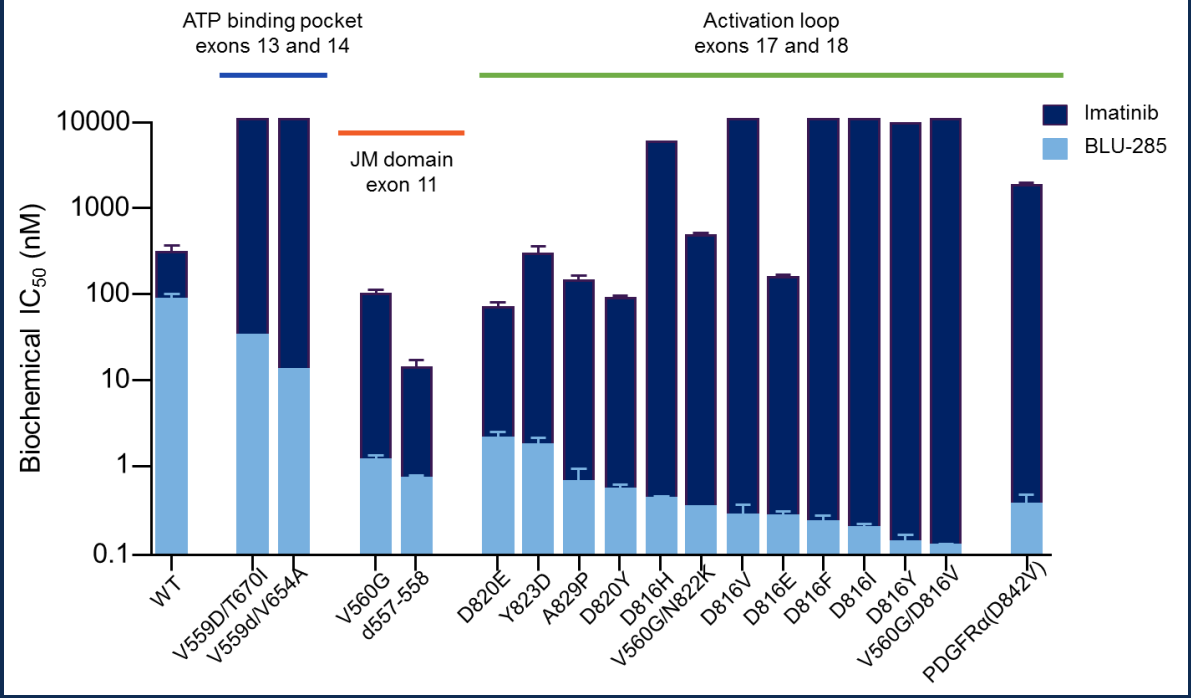


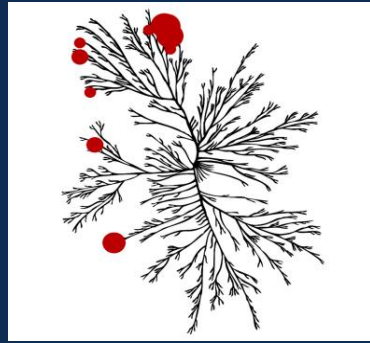
	Prevalence[7,8]	
Resistance mutation	**Primary**	**Secondary**
PDGFRα D842V	**~5–6%**	**Rare**
KIT exon 17/18	**~1%**	**2L ~23% ≥3L ~90%**
KIT exon 13	**N/A**	**2L ~40%**

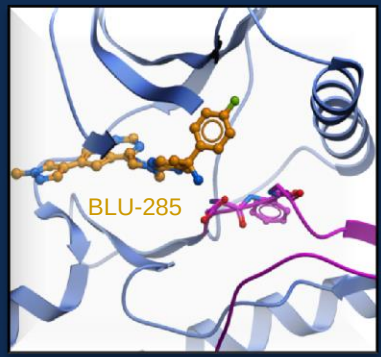
- Primary and secondary mutations cause therapeutic resistance
- Approved agents are ineffective against PDGFRα D842V

*Imatinib re-challenged

BLU-285: highly potent and selective targeting of KIT/PDGFRα GIST mutants





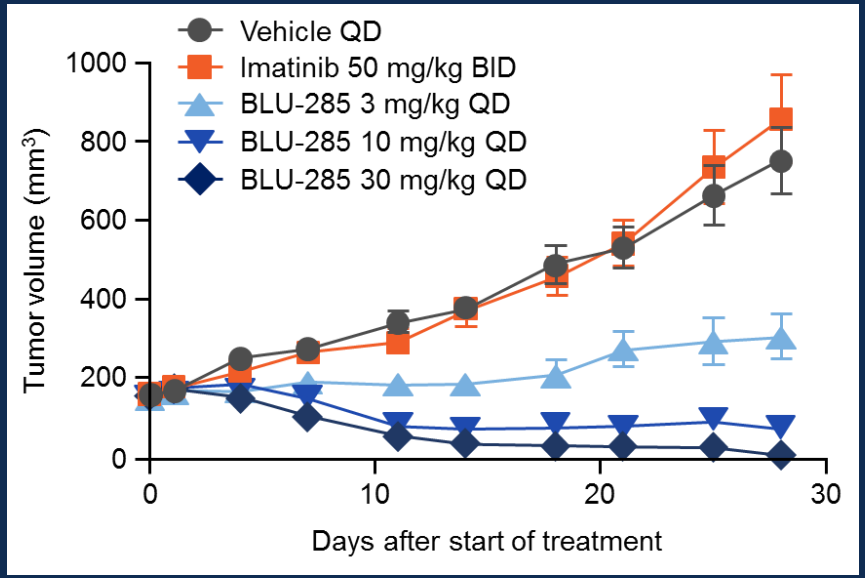


- High kinome selectivity*
- Binds active conformation

*Image reproduced courtesy of CSTI (www.cellsignal.com)

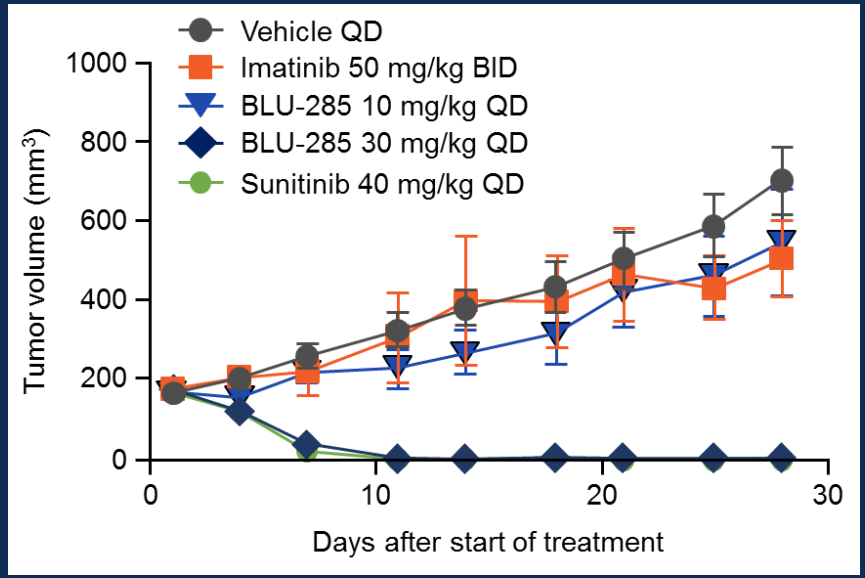
BLU-285: highly active against imatinib-resistant GIST patient derived xenografts

KIT exon 11/17 mutant



- Tumor regression at 10 and 30 mg/kg QD

KIT exon 11/13 mutant

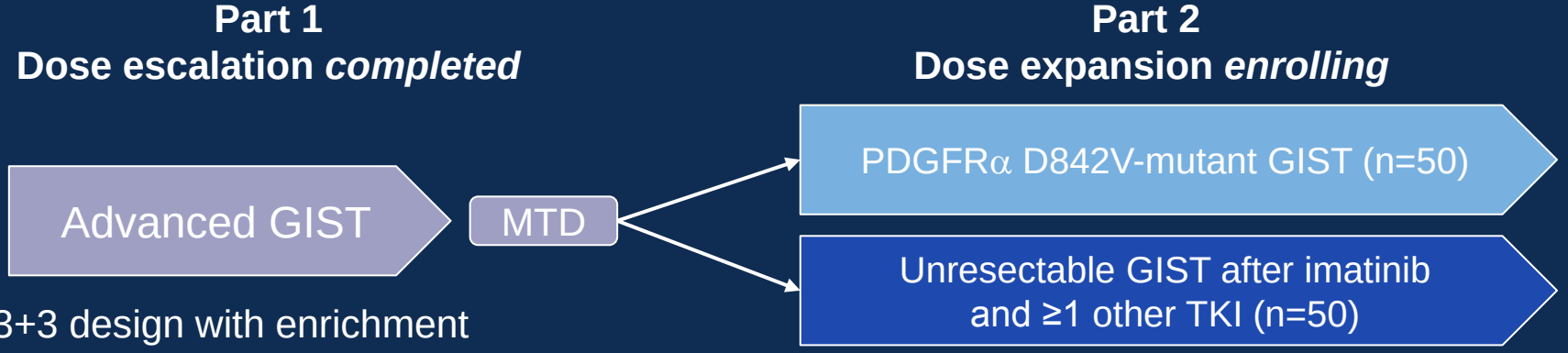


- Tumor regression at 30 mg/kg QD

BLU-285 Phase 1 study

Key objectives

- Part 1: MTD, safety, pharmacokinetics, ctDNA analyses, anti-tumor activity
- Part 2: response rate, duration of response, safety



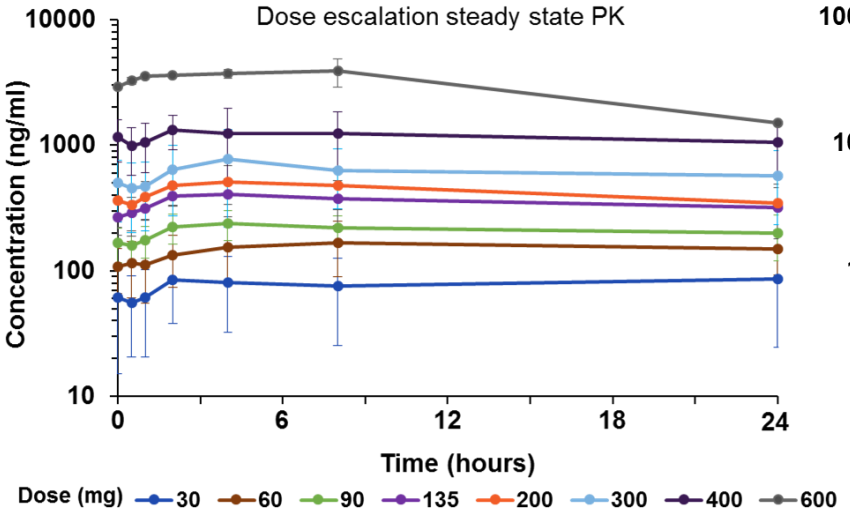
- 3+3 design with enrichment
- Dose levels: 30, 60, 90, 135, 200, 300, 400 and 600 mg QD
- MTD determined to be 400 mg PO QD

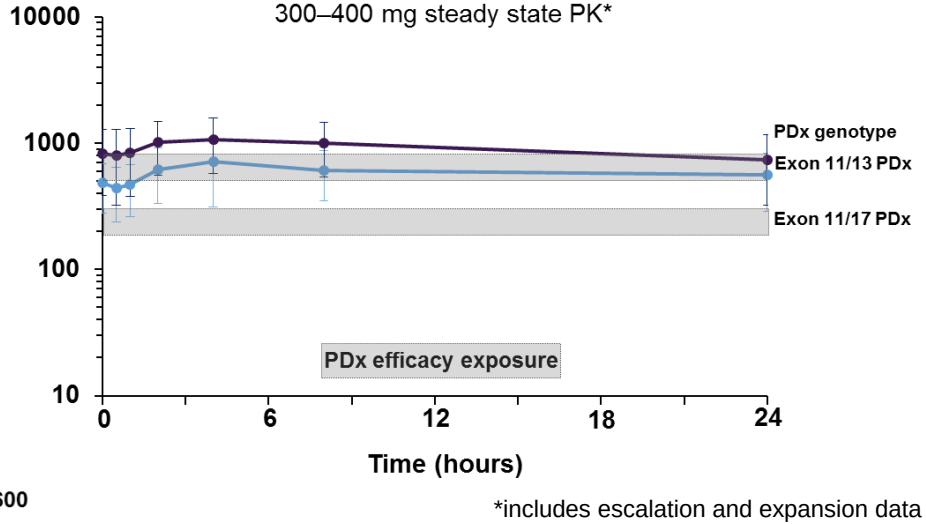
Demography and baseline patient characteristics

Parameter	All patients, N=72	
Age (years), median (range)	61 (25–85)	
	n (%)	
GIST subtype		
KIT mutant	40 (56)	
PDGFRα mutant	32 (44)	
Metastatic disease	69 (96)	
Largest target lesion size (cm)		
≤5	18 (25)	
>5–≤10	25 (35)	
>10	29 (40)	
No. prior kinase inhibitors	PDGFRα	KIT
Median (range)	1.5 (0–6)	4 (2–11)
≥3	10 (31)	36 (90)
Prior regorafenib	8 (25)	34 (85)

Data are preliminary and based on a cut off date of 28 April 2017

BLU-285 pharmacokinetics support QD dosing and broad mutational coverage



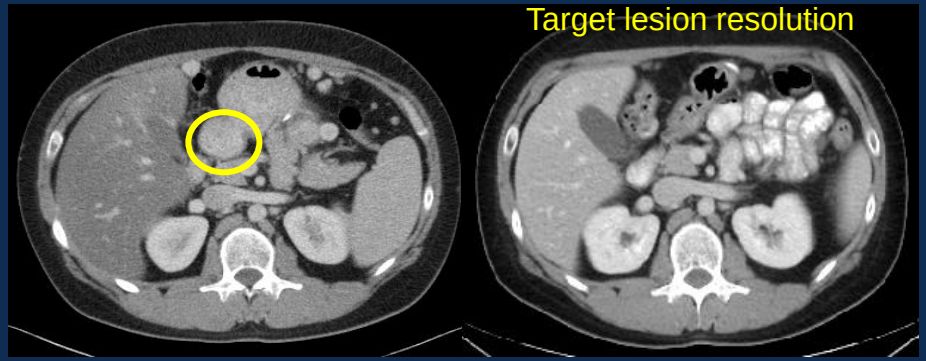


*includes escalation and expansion data

- Relatively rapid absorption Tmax ~2–8 hours and long half-life >24 hours
- Exposure at the 300 and 400 (MTD) mg provides broad coverage of primary and secondary KIT/PDGFRα mutations based on patient derived xenografts (PDX)

Radiographic response per RECIST 1.1 in PDGFRα D842V-mutant GIST

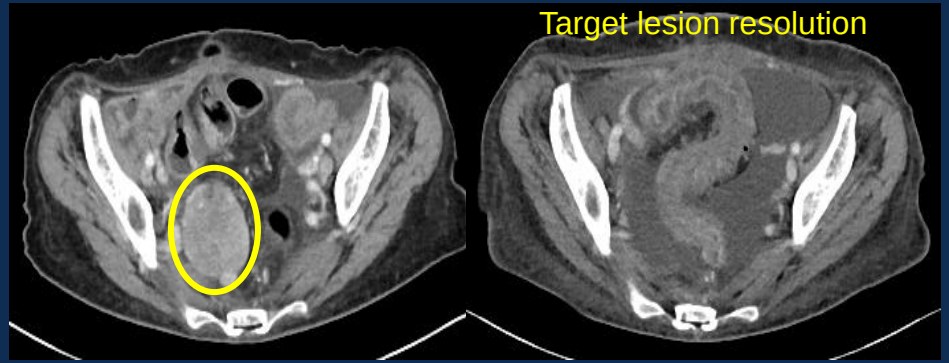
BLU-285 300 mg (dose escalation)



Baseline | After 4 months

- Ongoing at cycle 5
- Prior imatinib and sunitinib
- Confirmed PR, -63% target sum

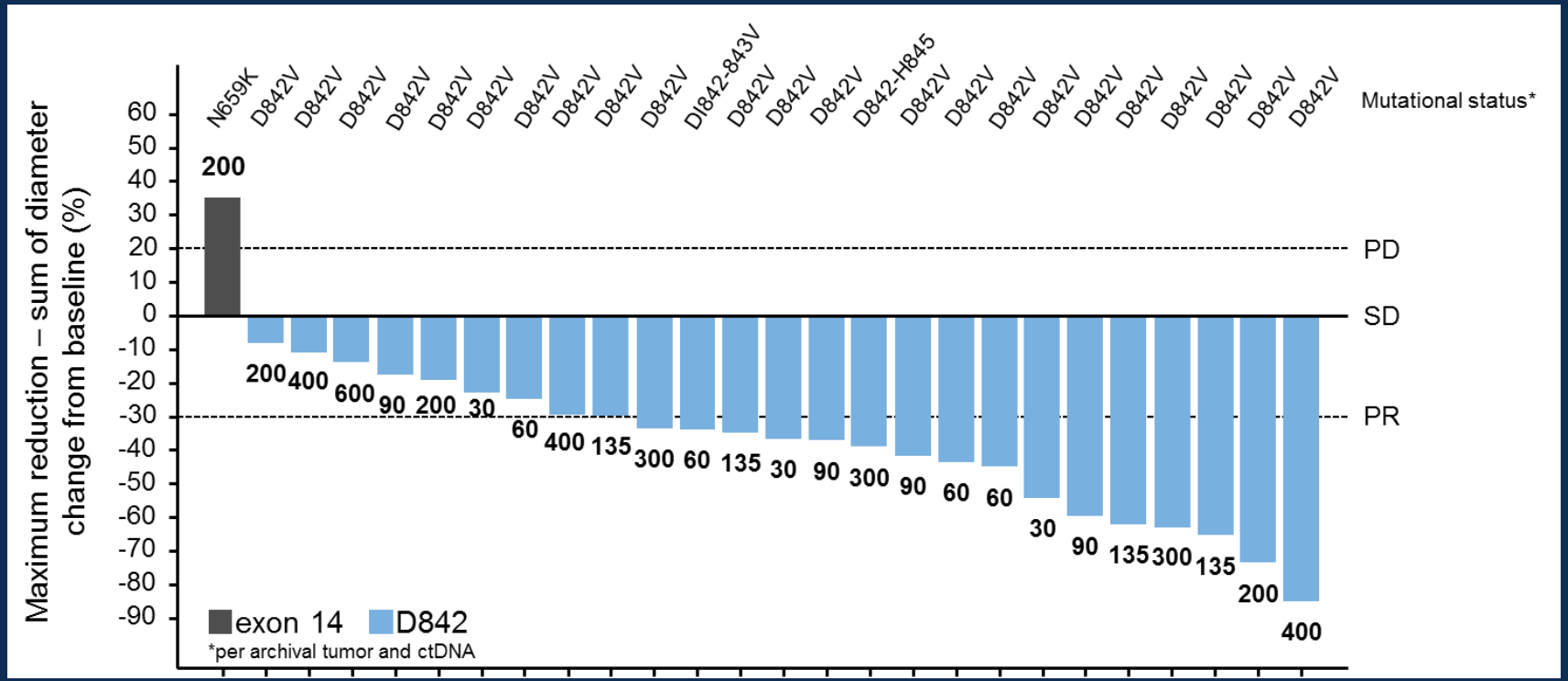
BLU-285 400 mg (dose expansion)



Baseline | After 2 months

- Ongoing at cycle 3
- Prior imatinib
- PR (pending confirmation), -85% target sum

Tumor regression across all dose levels in PDGFRα D842-mutant GIST (central radiology review)



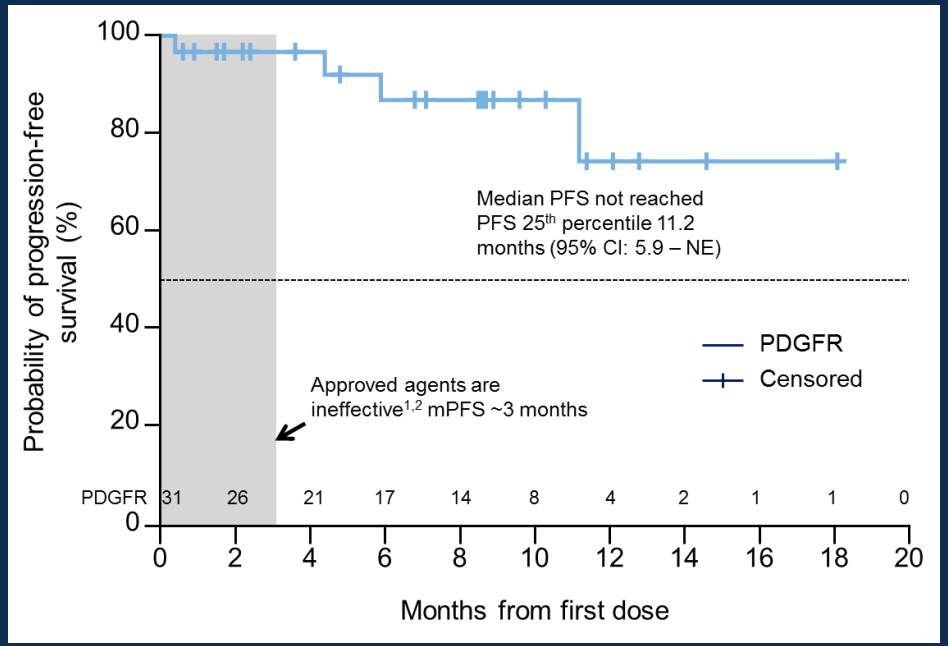
High response rate and prolonged PFS in PDGFRα D842-mutant GIST

Central radiographic review

Best response (N=25)	Choi Criteria n (%)	RECIST 1.1 n (%)
PR	25 (100%)	15* (60%)
SD	0	10 (40%)
DCR (PR + SD)	25 (100%)	25 (100%)
PD	0	0

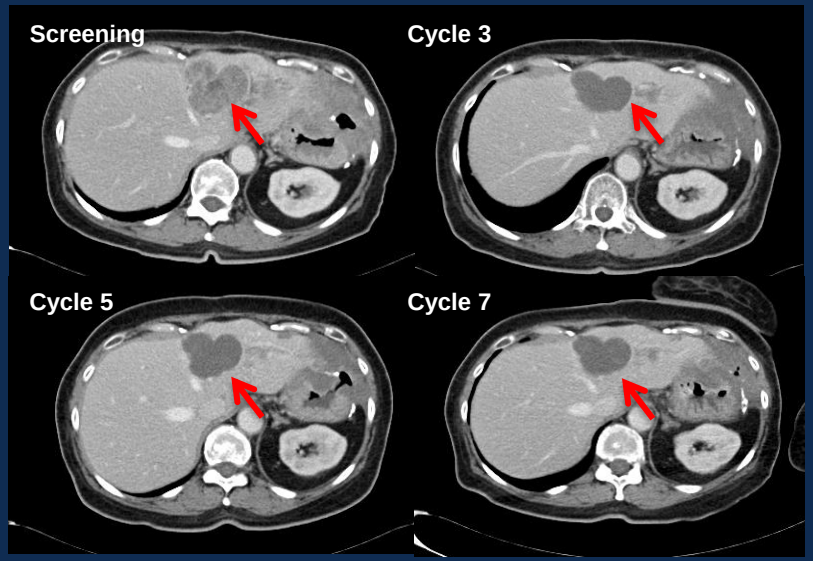
* 12 confirmed, 3 pending confirmation

- Approved agents are ineffective[1,2]
  - ORR ~0%



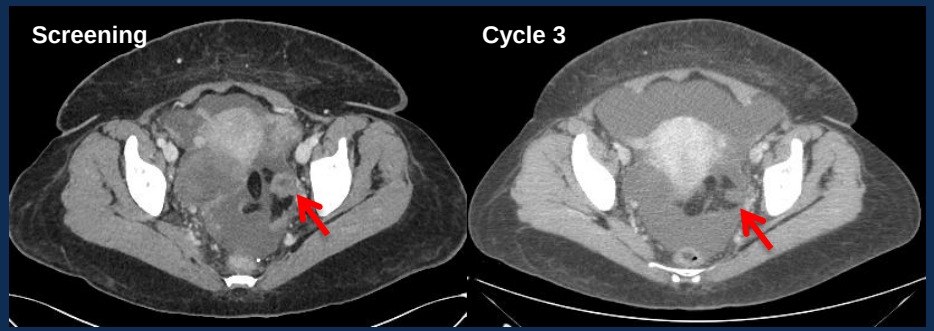
Radiographic response in heavily pre-treated KIT-mutant GIST

BLU-285 300 mg (dose escalation)



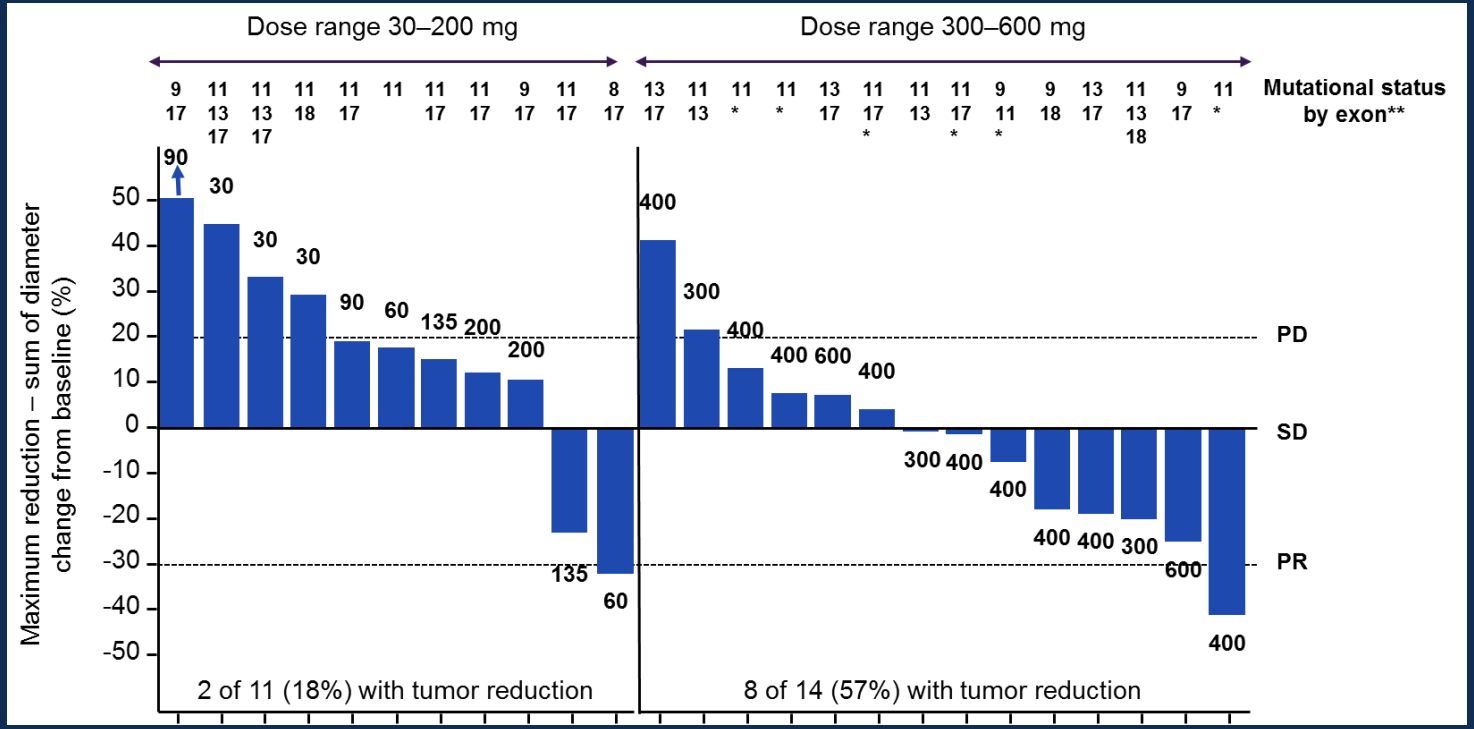
- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI PR (density -53%); RECIST SD (-21%)

BLU-285 400 mg (dose expansion)



- Ongoing at cycle 4
- 5 prior TKIs; 1° exon 11 mutation; ctDNA pending
- CHOI PR (density -76%); RECIST PR (-41%)

Dose-dependent tumor reduction across multiple KIT genotypes (central radiographic review)



*ctDNA results pending

**per archival tumor and ctDNA

Important clinical activity in heavily pre-treated KIT-mutant GIST

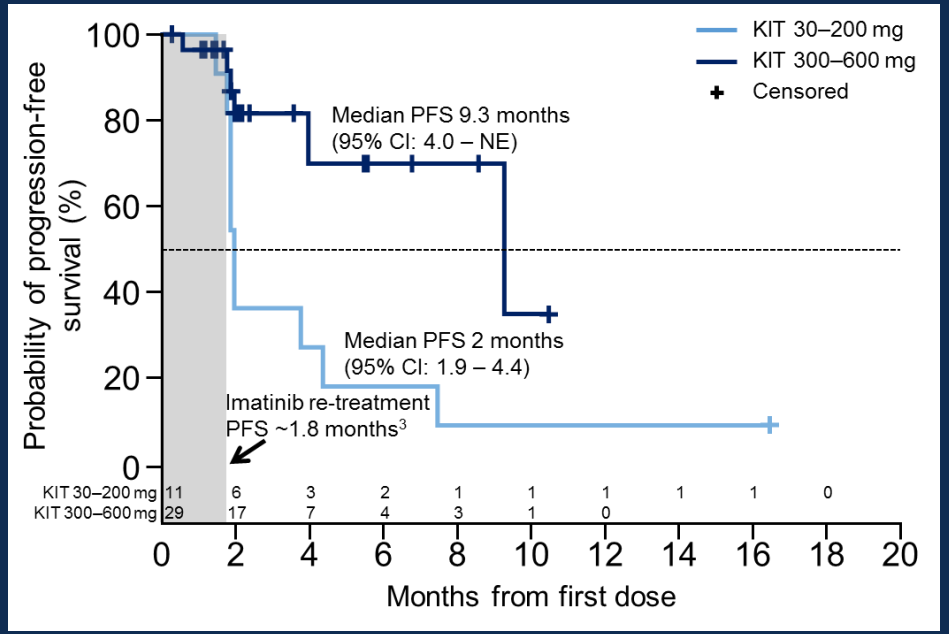
Central radiographic review

Best response (N=25)	Choi Criteria n (%)	RECIST 1.1 n (%)
PR	8 (32)	2* (8)
SD	6 (24)	12 (48)
DCR (PR + SD)	14 (56)	14 (56)
PD	11 (44)	11 (44)

* 1 confirmed, 1 pending confirmation

- Beyond third-line regorafenib there are no approved therapies
  - Imatinib re-treatment in ≥third-line GIST[3]
    - ORR ~0%

↑ PFS with BLU-285 ≥300 mg



Adverse events (AE) associated with BLU-285

Safety population, N=72		Severity, n (%)			
AEs in ≥20% of patients	n (%)	Grade 1	Grade 2	Grade 3	Grade 4/5
Nausea	43 (60)	31 (43)	9 (13)	3 (4)	0
Fatigue	38 (53)	16 (22)	16 (22)	6 (8)	0
Vomiting	30 (42)	21 (29)	6 (8)	3 (4)	0
Periorbital edema	26 (36)	22 (31)	4 (6)	0	0
Diarrhea	24 (33)	19 (26)	4 (6)	1 (1)	0
Edema peripheral	22 (31)	18 (25)	4 (6)	0	0
Decreased appetite	20 (28)	15 (21)	4 (6)	1 (1)	0
Anemia	18 (25)	4 (6)	8 (11)	6 (8)	0
Lacrimation increased	17 (24)	12 (17)	5 (7)	0	0
Dizziness	16 (22)	13 (18)	3 (4)	0	0

- 18 (25%) patients had Grade (G) ≥3 treatment-related (Fatigue [8%], hypophosphatemia [6%], anemia [4%], nausea, vomiting, hyperbilirubinemia [3% each])
- DLT in 2 patients at 600 mg: 1 G2 hyperbilirubinemia; 1 G2 rash, hypertension, memory impairment
- BLU-285 discontinuations: disease progression n=19, treatment-related toxicity (G3 hyperbilirubinemia) n=1, and investigator's decision n=1

Conclusions

- BLU-285 is well tolerated on a QD schedule at doses up to the MTD of 400 mg
- Exposure at 300–400 mg QD provides broad coverage of primary and secondary KIT / PDGFRα mutants
- BLU-285 has strong clinical activity in PDGFRα D842-mutant GIST with an ORR of 60% per central review and median PFS not reached
  - Potential expedited paths for approval are being evaluated
- BLU-285 demonstrates important anti-tumor activity including radiographic response and prolonged PFS in heavily pre-treated, KIT-mutant GIST at doses of 300–400 mg QD
  - Based on these encouraging data, planning is underway for a Phase 3 randomized study of BLU-285 in third-line GIST

Acknowledgments

We thank the participating patients, their families, all study co-investigators, and research coordinators at the following institutions:

- Oregon Health & Sciences University
- Royal Marsden Hospital/Institute for Cancer Research
- Leuven Cancer Institute
- University of Essen
- Fox Chase Cancer Center
- Erasmus MC Cancer Institute
- Centre Leon Berard
- Institut Gustave Roussy
- Dana-Farber Cancer Institute

We also thank Sarah Jackson, PhD, of iMed Comms, an Ashfield company, who provided editorial writing support funded by Blueprint Medicines

References

1. Cassier et al. *Clin Cancer Res*. 2012;18(16):4458–64
2. Yoo et al. *Cancer Res Treat*. 2016;48(2):546–52
3. Kang et al. *Lancet Oncol*. 2013;14(12):1175–82
4. National Comprehensive Cancer Network. Gastrointestinal Stromal Tumors. 2016
5. Demetri et al. *Lancet.* 2006;*368:1329*
6. Demetri et al. *Lancet.* 2013;*381:295-302*
7. Corless et al. *J Clin Oncol*. 2005;*23:5357*
8. Barnett and Heinrich. *Am Soc Clin Onc* Ed Book. 2012;663