Clinical activity of BLU-285, a highly potent and selective KIT/PDGFRα inhibitor designed to treat gastrointestinal stromal tumor (GIST)

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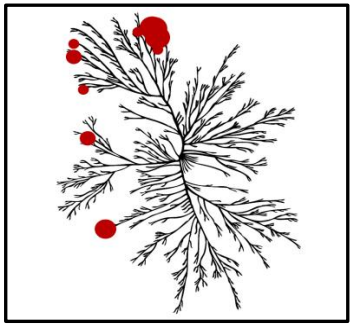
Abstract no: 2803523, CTOS 2017 Maui, Hawaii. Presented by Dr. Michael Heinrich

Disclosures

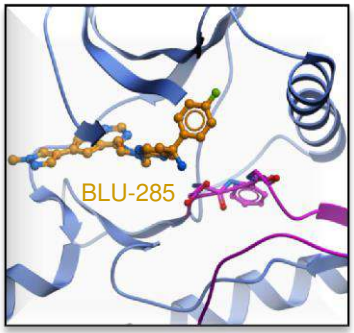
- BLU-285 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
- Dr. Michael Heinrich is an investigator for Blueprint Medicines' ongoing Phase 1 study in unresectable gastrointestinal stromal tumor
- Dr. Michael Heinrich has the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

BLU-285: highly selective targeting and potent inhibition of mutant KIT and PDGFRα in GIST

		BLU-285 IC_{50}	Imatinib IC_{50}
KIT Exon 11 deletion	JM domain mutations	0.6 nM	12 nM
KIT Exon 11 V560G		1 nM	87 nM
KIT Exon 11/13	ATP binding site mutations	11 nM	9160 nM
KIT Exon 11/14		28 nM	19650 nM
KIT Exon 17	Activation loop mutations	<2 nM	60–12750 nM
KIT Exon 17 D816V		0.27 nM	8150 nM
PDGFRα Exon 18 D842V		0.24 nM	759 nM



• High kinome selectivity*



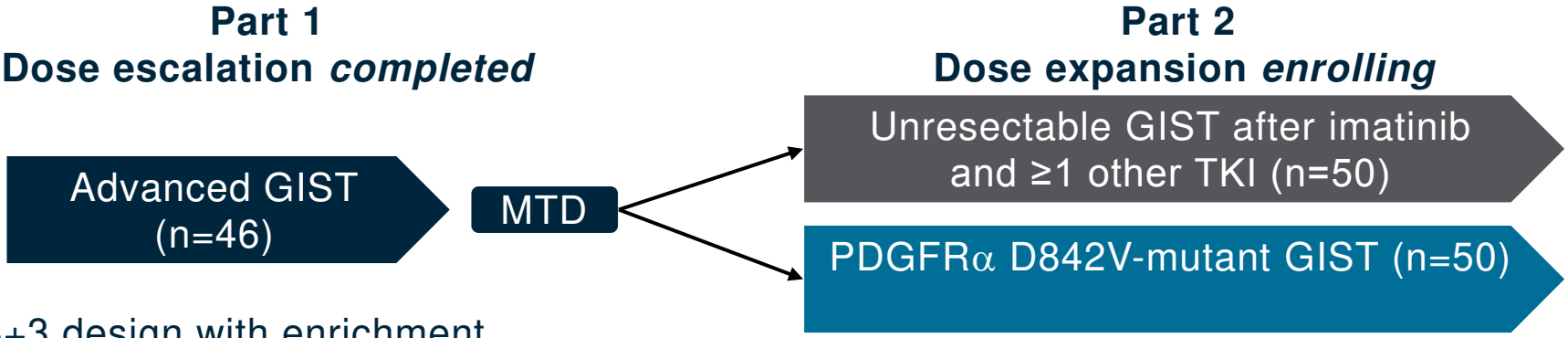
• Binds active conformation

1. Evans EK et al. Sci Transl Med. 2017 Nov 1;9(414)
*Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)

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
- MTD determined to be 400 mg PO QD
- RP2D determined to be 300 mg PO QD

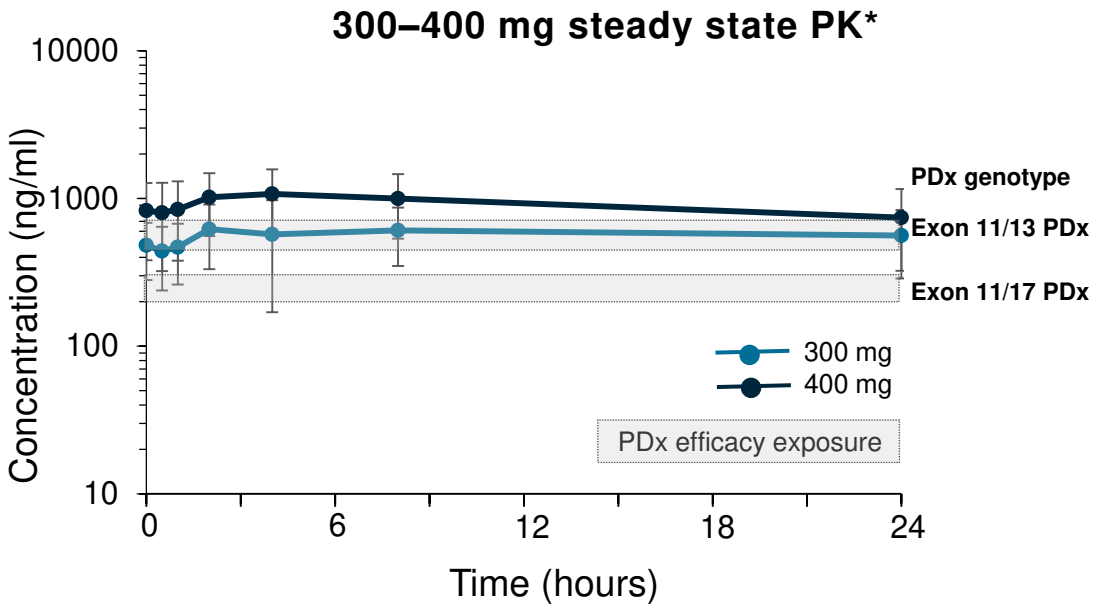
MTD, maximum tolerated dose; RP2D, recommended Phase 2 dose

Demography and baseline patient characteristics

Parameter	All patients, N=116	
Age (years), median (range)	62 (25–85)	
	n (%)	
GIST subtype*		
KIT mutant	76 (66)	
PDGFRα D842 mutant	37 (32)	
PDGFRα Exon 14 (N659K) mutant	2 (2)	
KIT & PDGFRα WT	1 (1)	
Metastatic disease	107 (92)	
Largest target lesion size (cm)		
≤5	27 (23)	
>5–≤10	42 (36)	
>10	46 (40)	
pending	1 (1)	
No. prior kinase inhibitors	PDGFRα	KIT
Median (range)	1 (0–6)	4 (2–11)
≥3	11 (28)	67 (87)
Prior regorafenib	8 (21)	64 (83)

* Data are preliminary and based on a cut off date of 11 Oct 2017

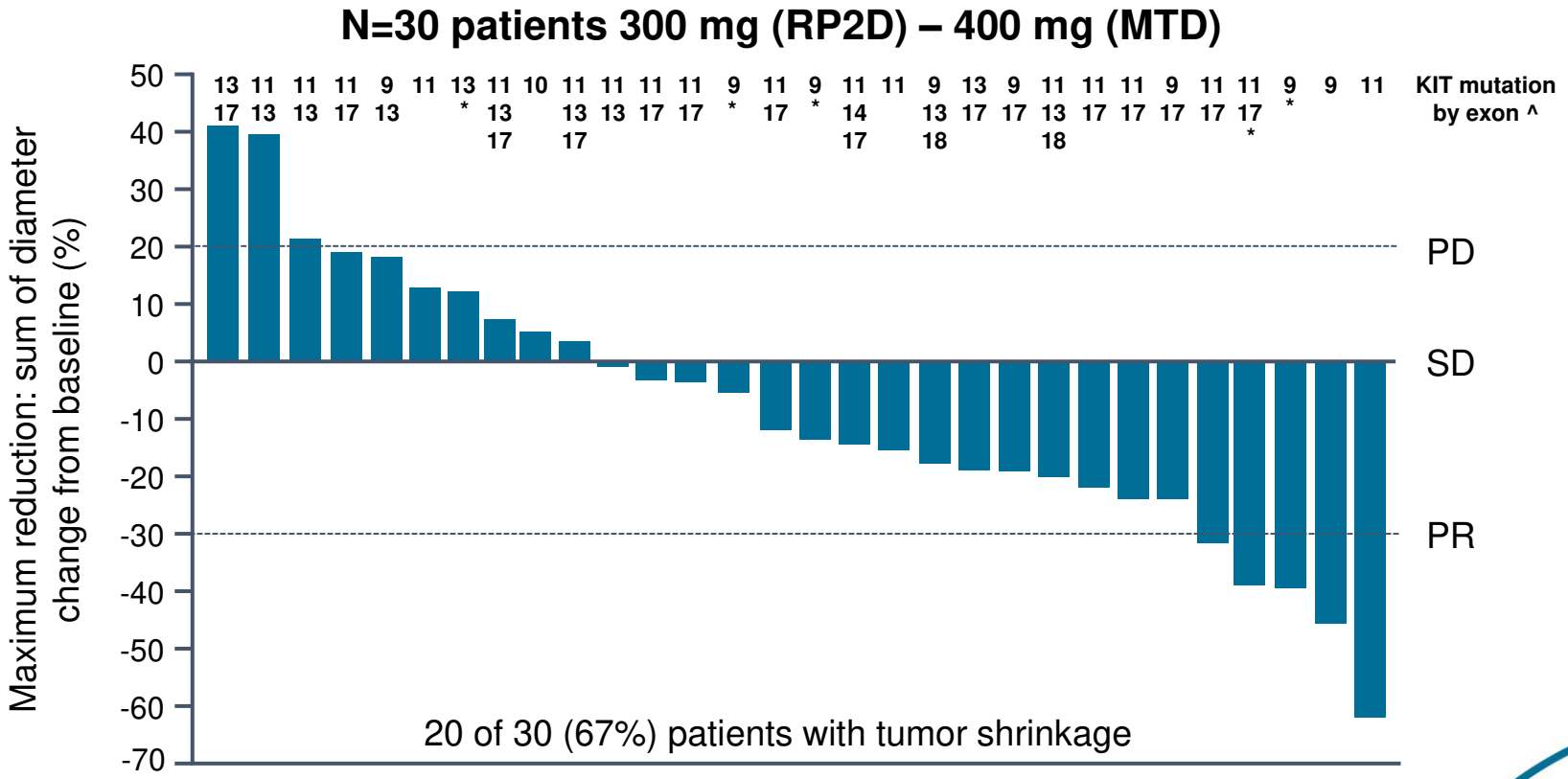
BLU-285 pharmacokinetics support once daily dosing and broad mutational coverage



- Relatively rapid absorption median Tmax 4–6 hours, dose-proportional exposure and long half-life >24 hours
- 300 mg selected as RP2D based on safety, PK, anti-tumor activity

*Includes escalation and expansion data

Tumor reduction across multiple KIT genotypes (central radiology review)



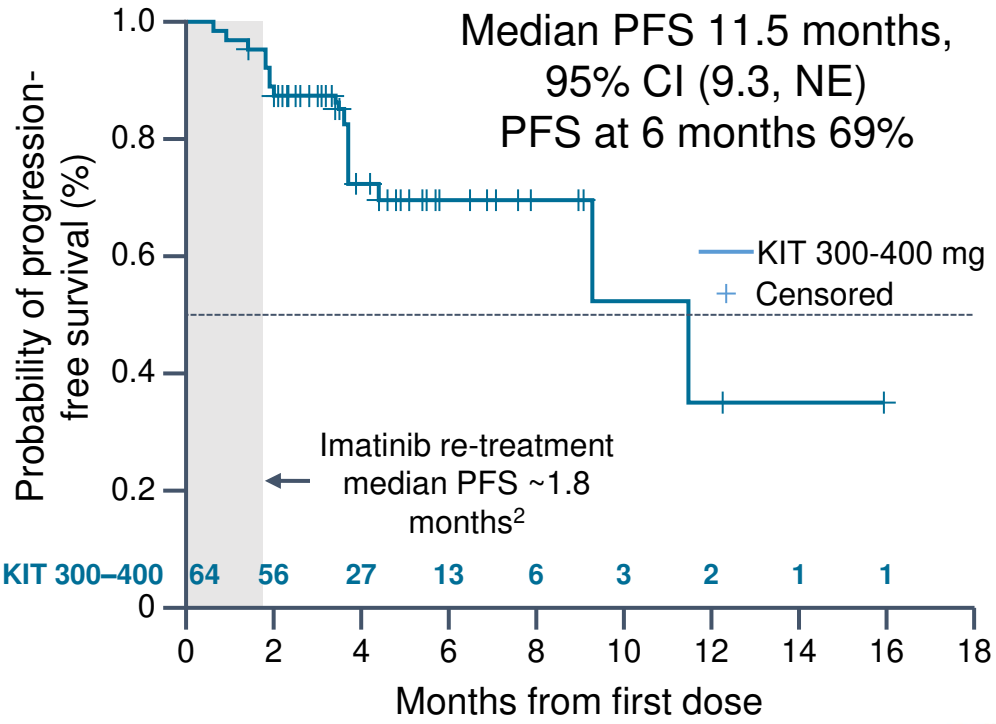
* ctDNA results pending; ^ per archival tumor and ctDNA

Prolonged PFS in heavily pre-treated KIT-mutant GIST (central radiology review)

Best response (N=30)*	Choi Criteria n (%)	RECIST 1.1 n (%)
PR	16 (53)	5 (17)^
SD	7 (23)	18 (60)
DCR (PR+SD)	23 (77)	23 (77)
PD	7 (23)	7 (23)

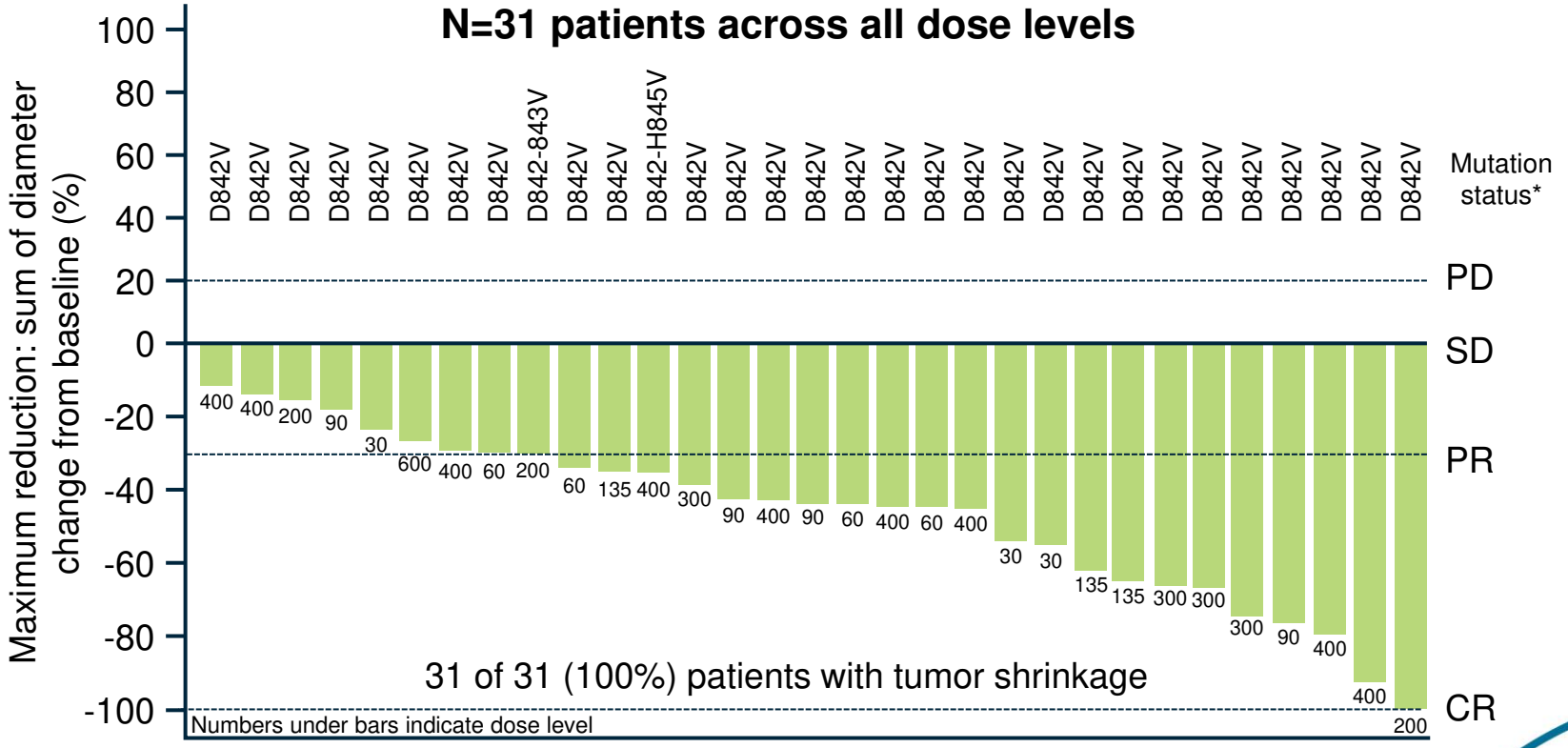
*300 RP2D–400 MTD mg; ^2 pending confirmation

- No approved therapies beyond third-line regorafenib
  - ORR ~0% with imatinib re-treatment in ≥third-line[2]



2. Kang et al. Lancet Oncol. 2013;14(12):1175–82

Remarkable activity in PDGFRα D842-mutant GIST (central radiology review)

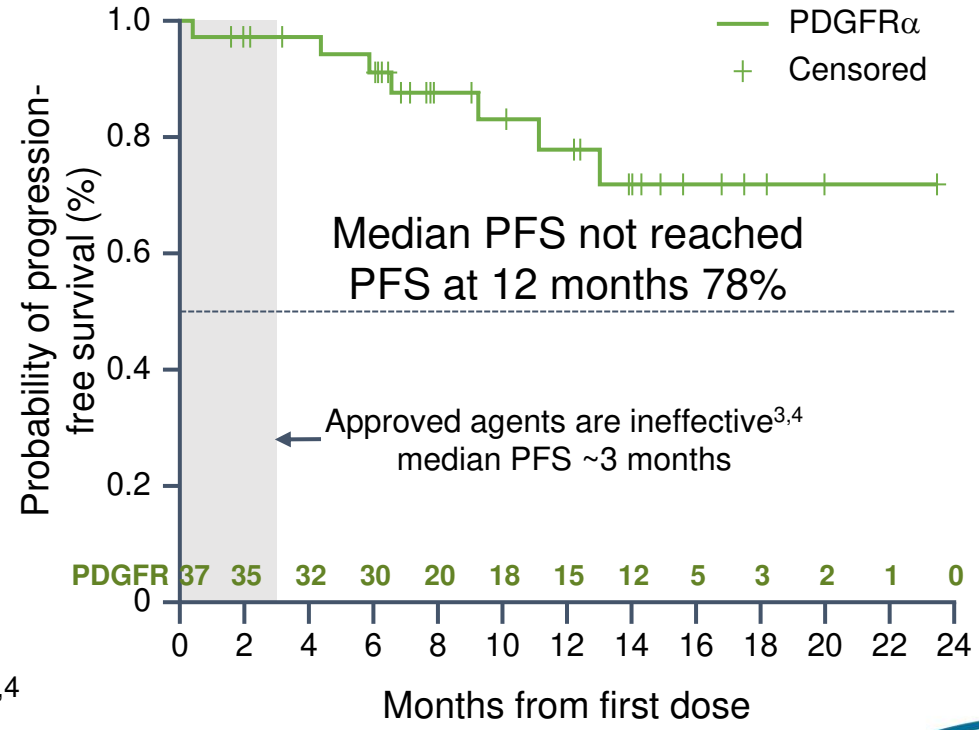


* per archival tumor and ctDNA

High response rate and prolonged PFS in PDGFRα D842-mutant GIST (central radiology review)

Best response (N=31)*	Choi Criteria n (%)	RECIST 1.1 n (%)
CR	1 (3)	1 (3)^
PR	30 (97)	21 (68)†
CR+PR	31 (100)	22 (71)
SD	0	9 (29)
DCR (PR+SD)	31 (100)	31 (100)
PD	0	0

*All dose levels included
^PR from C3 to C13, CR at C16, CR pending confirmation
†3 pending confirmation



- ORR ~0% with currently approved agents[3,4]

3. Cassier et al. Clin Cancer Res. 2012;18(16):4458–64
4. Yoo et al. Cancer Res Treat. 2016;48(2):546–52

Treatment emergent adverse events ≥20%

Safety population (all patients) N=116		Severity				
Preferred Term, n (%)	**Any AE**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nausea	65 (56)	41 (35)	17 (15)	7 (6)	0	0
Fatigue	62 (53)	23 (20)	31 (27)	8 (7)	0	0
Periorbital edema	50 (43)	42 (36)	8 (7)	0	0	0
Vomiting	48 (41)	36 (31)	9 (8)	3 (3)	0	0
Edema peripheral	39 (34)	28 (24)	9 (8)	2 (2)	0	0
Anemia	36 (31)	7 (6)	10 (9)	17 (15)	2 (2)	0
Diarrhea	36 (31)	26 (22)	8 (7)	2 (2)	0	0
Cognitive Effects*	35 (30)	20 (17)	10 (9)	4 (3)	1 (1)	0
Lacrimation increased	35 (30)	29 (25)	6 (5)	0	0	0
Decreased appetite	33 (28)	24 (21)	6 (5)	3 (3)	0	0
Dizziness	27 (23)	21 (18)	6 (5)	0	0	0
Constipation	25 (22)	18 (16)	6 (5)	0	1 (1)	0
Hair color changes	25 (22)	24 (21)	0	0	0	0

* Consists of multiple similar AEs that have been aggregated into a single category. 42% of patients at 400 mg (MTD), 18% of patients at 300 mg (RP2D).

- 39 (34%) patients had grade ≥3 treatment-related AEs: anemia (9%), fatigue (7%), hypophosphatemia (4%), nausea (4%), cognitive effects (3%)
- 67 patients on treatment; 49 discontinued: PD n=40, AEs n=6, withdrew consent n=3

BLU-285 has potent, clinically important activity in GIST

- BLU-285 is well-tolerated at the 300 mg RP2D and provides broad mutational coverage
- Remarkable response rates and prolonged PFS in PDGFRα-driven GIST may support expedited approval path
- Prolonged PFS in heavily pretreated KIT-driven GIST warrants further study, expanding current cohort to 100 patients
- Based on these encouraging data:
  - Second-line expansion cohort has been added and sites are open
  - Phase 3 randomized study comparing BLU-285 to regorafenib in third-line GIST is planned to begin in 1H 2018

Acknowledgments

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

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

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