Advances in GIST

2017 ASCO Annual Meeting

Monday, June 5, 2017

Forward-looking statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

In this presentation, forward-looking statements include, without limitation, statements about plans and timelines for the clinical development of BLU-285, BLU-554 and BLU-667 and the ability of Blueprint Medicines Corporation (the “Company”) to implement those clinical development plans; the potential benefits of the Company’s current and future drug candidates in treating patients; plans and timelines for regulatory submissions, filings or discussions; plans and timelines for the development and commercialization of companion diagnostics for the Company’s current or future drug candidates; plans and timelines for current or future discovery programs; plans and timelines for future collaborations, if any, with strategic partners; the future financial performance of the Company; expectations regarding potential milestones in 2017; and the Company’s strategy, business plans and focus. The Company has based these forward-looking statements on management’s current expectations, assumptions, estimates and projections. While the Company believes these expectations, assumptions, estimates and projections are reasonable, such forward-looking statements are only predictions and involve known and unknown risks, uncertainties and other important factors, many of which are beyond the Company’s control and may cause actual results, performance or achievements to differ materially from those expressed or implied by any forward-looking statements. These risks and uncertainties include, without limitation, risks and uncertainties related to the delay of any current or future clinical trials or the development of the Company’s drug candidates, including BLU-285, BLU-554 and BLU-667; the Company's advancement of multiple early-stage efforts; the Company’s ability to successfully demonstrate the efficacy and safety of its drug candidates; the preclinical and clinical results for the Company’s drug candidates, which may not support further development of such drug candidates; actions or decisions of regulatory agencies or authorities, which may affect the initiation, timing and progress of current or future clinical trials; the Company’s ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing; the Company’s ability to develop and commercialize companion diagnostics for its current and future drug candidates, including a companion diagnostic for BLU-554 with Vantaa Medical Systems, Inc. and a companion diagnostic for BLU-285 with QIAGEN Manchester Limited; and the success of the Company’s rare genetic disease collaboration with Alexion Pharma Holding and its cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc.

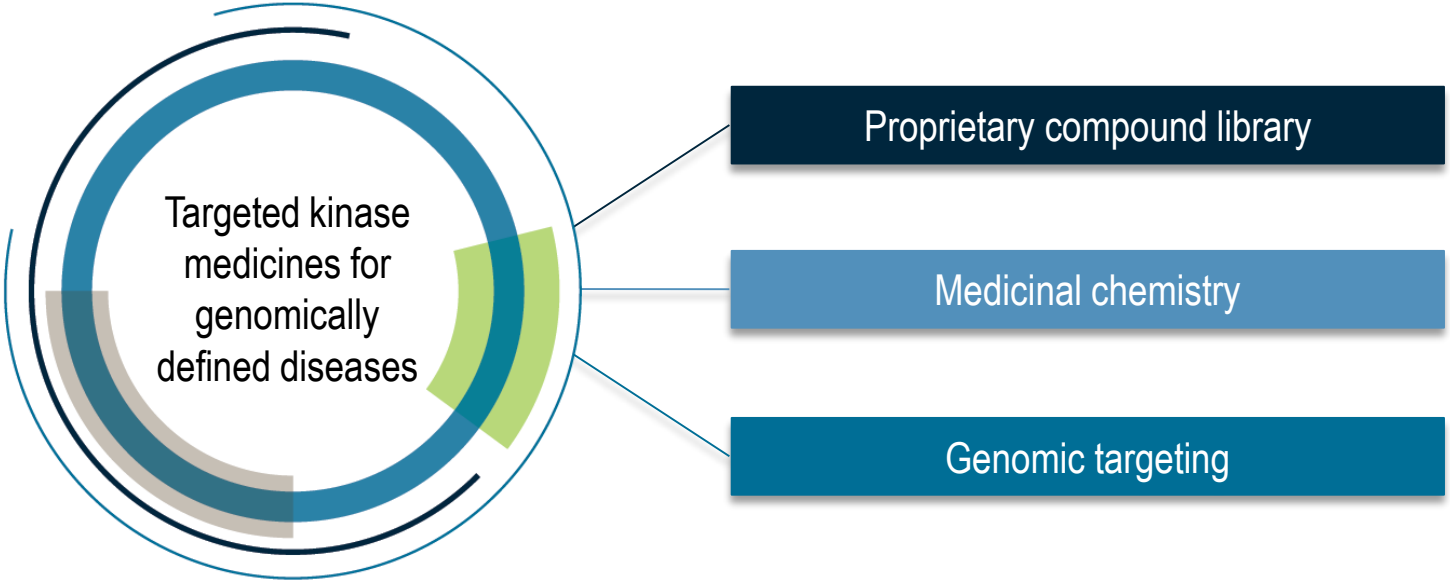
These and other risks and uncertainties are described in greater detail under “Risk Factors” in the Company’s Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, as filed with the Securities and Exchange Commission (“SEC”) on May 3, 2017, and any other filings the Company may make with the SEC in the future. The Company cannot guarantee future results, outcomes, levels of activity, performance, developments, or achievements, and there can be no assurance that the Company’s expectations, intentions, anticipations, beliefs, or projections will result or be achieved or accomplished. The forward-looking statements in this presentation are made only as of the date hereof, and except as required by law, the Company undertakes no obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise.

This presentation also contains estimates, projections and other statistical data made by independent parties and by the Company relating to market size and growth and other data about the Company’s industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of the Company’s future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

Agenda

Welcome	Jeff Albers, Chief Executive Officer, Blueprint Medicines
Overview of BLU-285 in GIST	Andy Boral, MD, Chief Medical Officer, Blueprint Medicines
Phase 1 clinical trial results	Michael Heinrich, MD, Professor, Oregon Health and Science University
Proposed registration path	Andy Boral, MD, Chief Medical Officer, Blueprint Medicines
Question and answer session	Michael C. Heinrich, MD, Professor, Oregon Health and Science University Jeff Albers, Chief Executive Officer, Blueprint Medicines Andy Boral, MD, Chief Medical Officer, Blueprint Medicines
Closing remarks	Jeff Albers, Chief Executive Officer, Blueprint Medicines

A blueprint for a healthier tomorrow

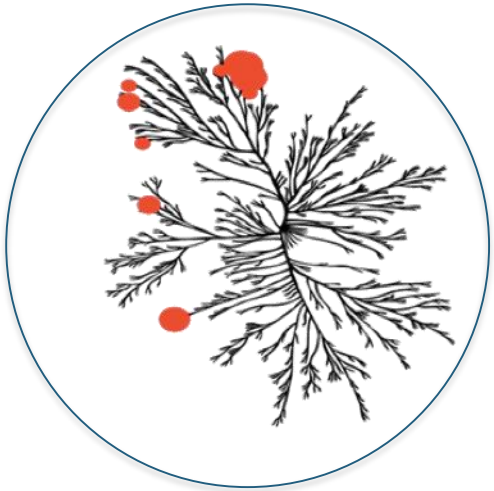


Discovery platform for exquisitely selective kinase inhibitors, matched to specific molecular drivers of disease, with rapid path to clinical proof-of-concept

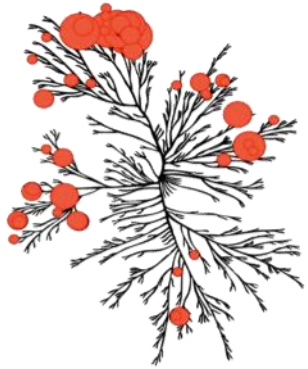
A new way of looking at kinase medicines

Sutent

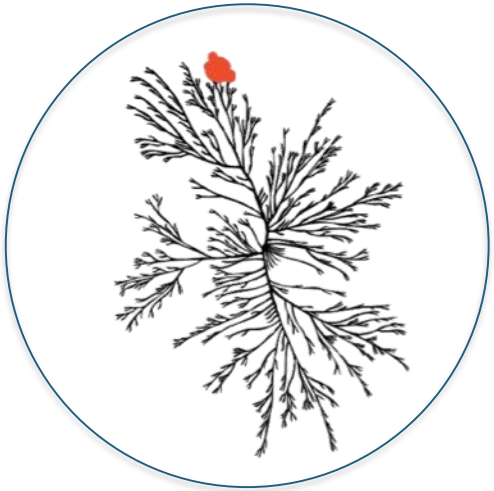
BLU-285



Nexavar



BLU-554



We aim to design and develop **highly targeted kinase medicines** with improved potency, less off-target activity, and a high probability of clinical success

Kinome illustration reproduced courtesy of CSTI (cellsignal.com). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content; IO, immuno-oncology

Three major areas of focus

Genomically defined cancers	Rare diseases	Cancer immunotherapy
Oncogenic kinases resulting from tumor genetic alterations	Abnormally activated kinases due to rare genetic alterations	Intracellular immunokinases involved in tumor immunity
• BLU-285 gastrointestinal stromal tumors • BLU-554 hepatocellular carcinoma • BLU-667 RET-altered cancers	• BLU-285 systemic mastocytosis • Alexion collaboration (1 target)	• Roche collaboration (up to 5 targets)

Robust pipeline of diverse clinical stage assets

DRUG CANDIDATE	DISCOVERY	PRECLINICAL	CLINICAL	COMMERCIAL RIGHTS
BLU-285 Inhibitor of KIT, including exon 17 mutations, and PDGFRα, including the D842V mutation			PHASE 1 - PDGFRα-DRIVEN GIST PHASE 1 - KIT-DRIVEN GIST PHASE 1 – SYSTEMIC MASTOCYTOSIS	
BLU-554 Inhibitor of FGFR4			PHASE 1 – HEPATOCELLULAR CARCINOMA	
BLU-667 Inhibitor of RET fusions, mutations and resistant mutants			PHASE 1 – NSCLC & THYROID*	
PRKACA Inhibitor of PRKACA fusions			FLC	
Cancer immunotherapy Immunokinases			UP TO 5 PROGRAMS, STAGE UNDISCLOSED**	Roche
Rare genetic disease			TARGET AND DEVELOPMENT STAGE UNDISCLOSED	ALEXION

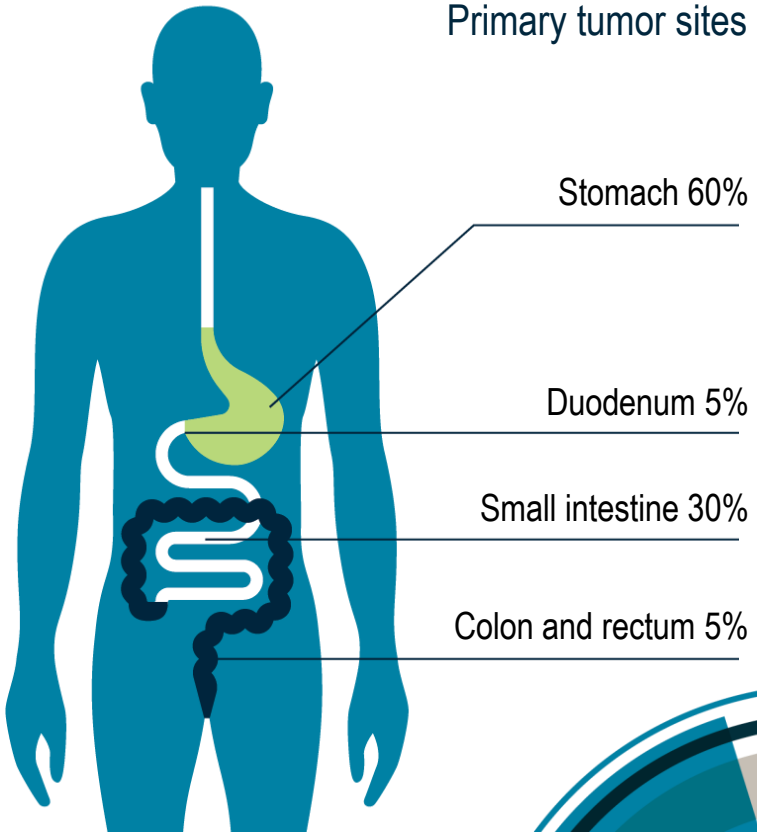
FLC, Fibrolamellar carcinoma; GIST, advanced gastrointestinal stromal tumors; NSCLC, non-small cell lung cancer. All Phase 1 clinical trials are in advanced disease.
*Phase 1 trial includes a basket cohort that consists of other advanced solid tumors with RET alterations.
**Blueprint Medicines has U.S. commercial rights for up to two programs. Roche has worldwide commercialization rights for up to three programs and ex-U.S. commercialization rights for up to two programs.

BLU-285 Drug Discovery Overview

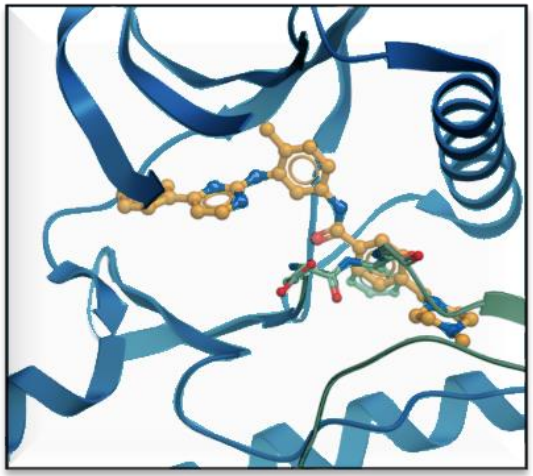
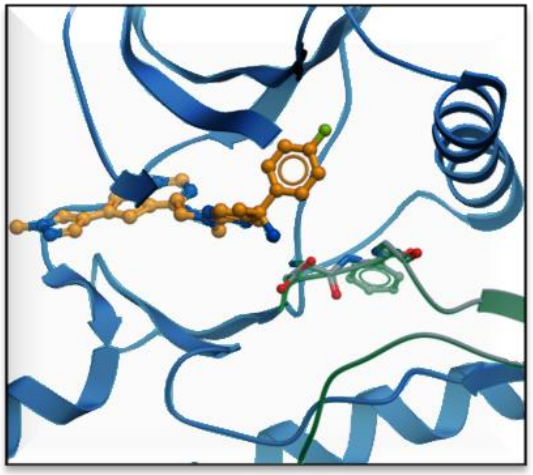
Andy Boral, M.D.
Chief Medical Officer

Gastrointestinal stromal tumors (GIST)

- Typically presents as stomach or intestinal mass
- Metastases in liver, peritoneum and other distant sites
- Mutant receptor tyrosine kinases are key disease drivers
  - PDGFRα ~5-10%
  - KIT ~75-80%
- Beyond imatinib, no highly effective treatments



PDGFRα and KIT activation loop mutations stabilize the kinase active conformation, blocking binding of type 2 inhibitors

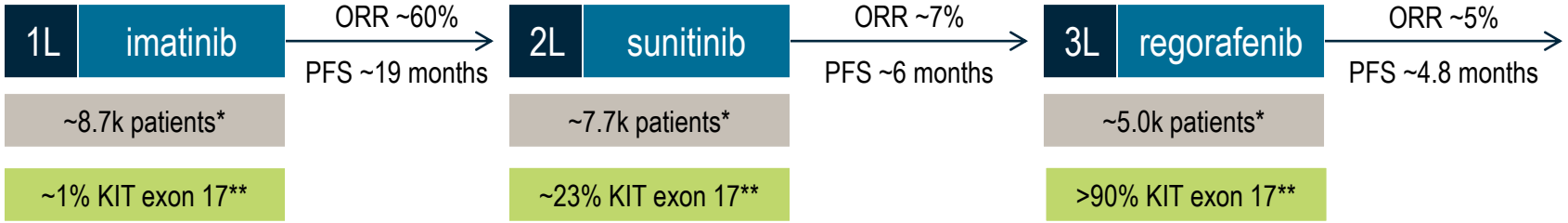
	Imatinib	BLU-285
Kinase in active conformation		

- Imatinib is a type 2 multikinase inhibitor that cannot bind the kinase active conformation due to a steric clash
- BLU-285 is a type 1 selective PDGFRα/KIT inhibitor that binds to the kinase active conformation

Currently available therapies do not effectively address activation loop mutations

PDGFRα D842V

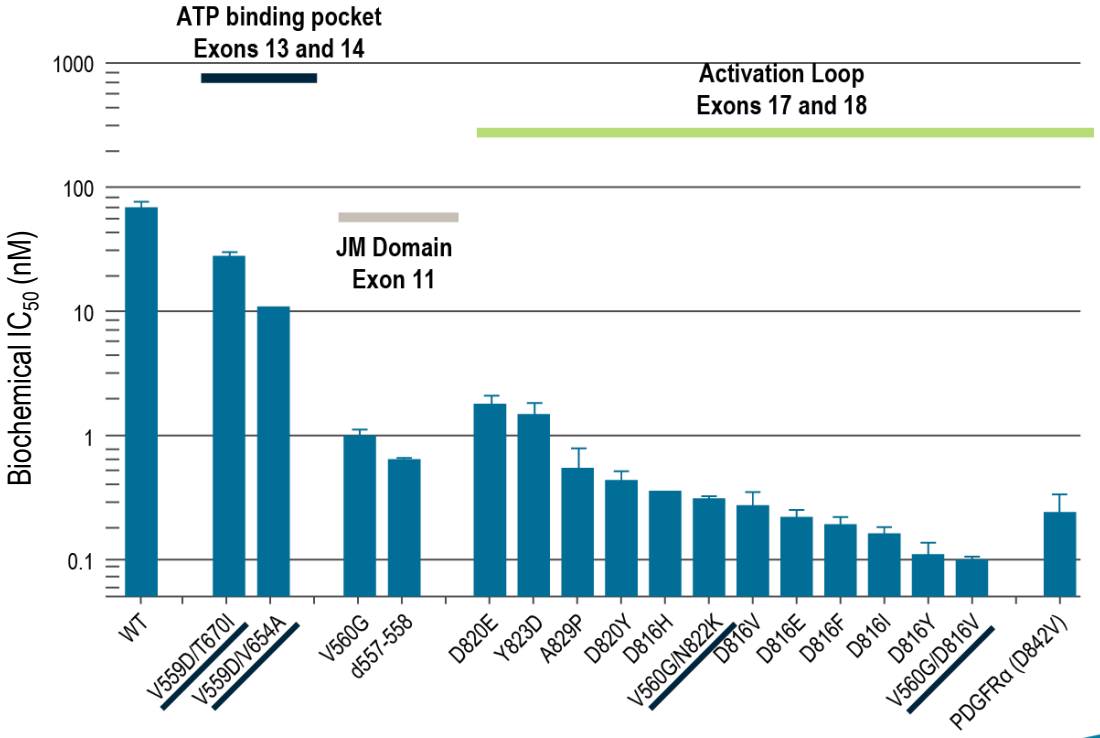
ALL GIST



*Estimated incidence for GIST patients in major markets (US, EU5 and Japan).
**Estimated frequency of Exon 17 activation loop mutations.

Promising preclinical data supported initiation of a Phase 1 clinical trial of BLU-285 in advanced GIST

- Most potent biochemical activity against activation loop mutants
- Biochemical activity across a broad PDGFRα and KIT mutational spectrum



Data previously presented in April 2017 at the AACR Annual Meeting

Updated Phase 1 clinical trial results

Michael C. Heinrich, M.D.
Oregon Health & Sciences University (OHSU)

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

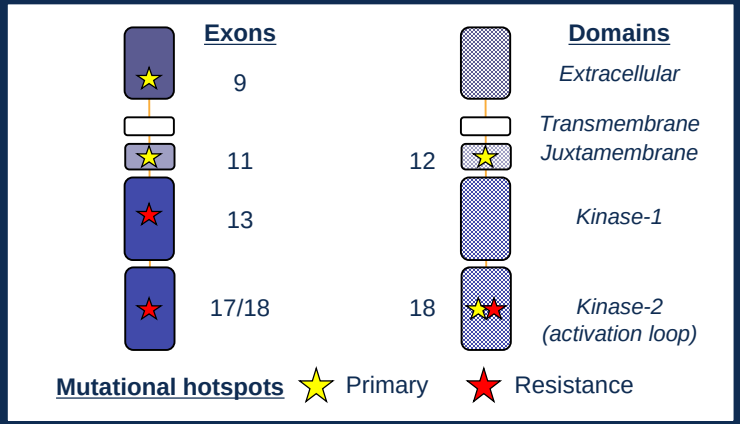
PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Abstract no: 11011 Presented by: Dr. Michael Heinrich

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

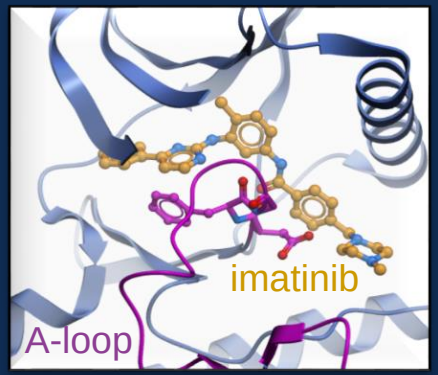
KIT PDGFRα



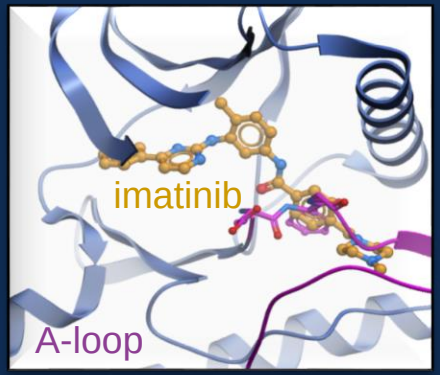
- KIT mutations drive ~75–80% of GIST
- PDGFRα mutations drive ~5–10% of GIST

KIT

Inactive conformation

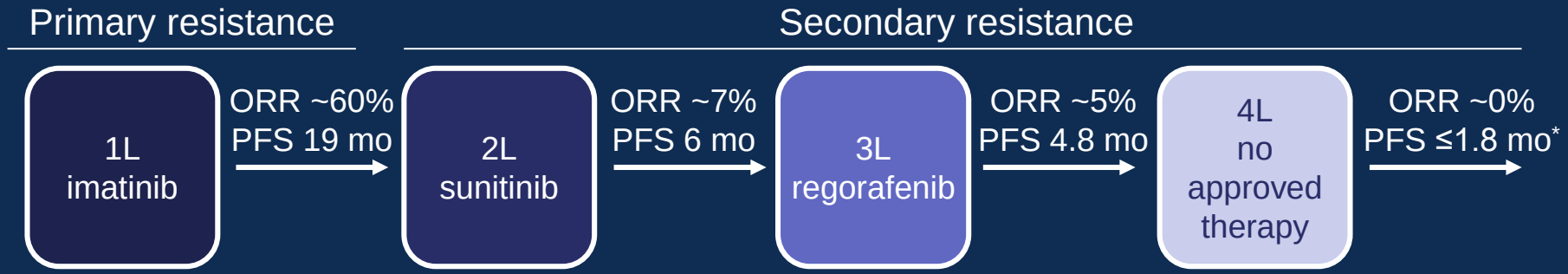


Active conformation



- 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]

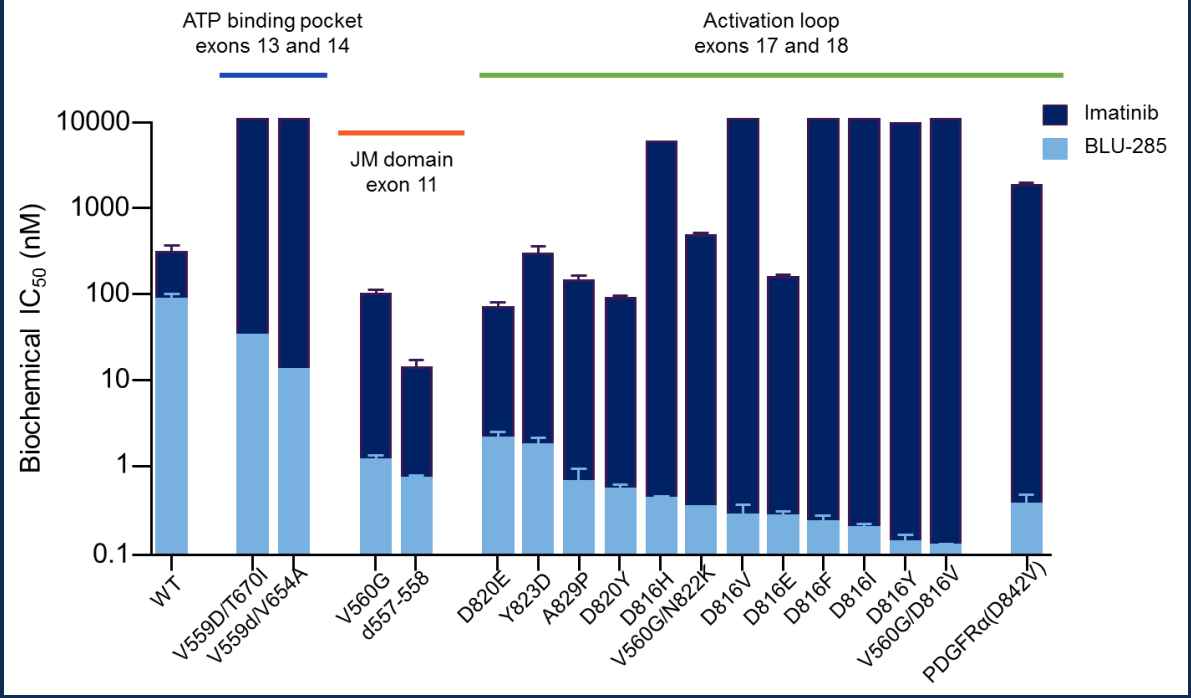


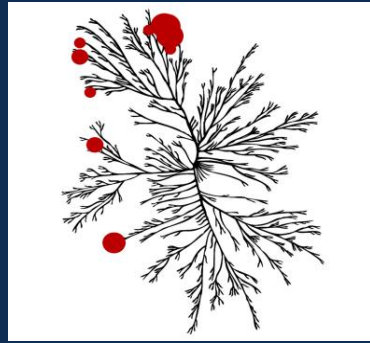
	Prevalence[7,8]	
Resistance mutation	**Primary**	**Secondary**
PDGFRα D842V	~5–6%	Rare
KIT exon 17/18	~1%	2L ~23% ≥3L ~90%
KIT exon 13	N/A	2L ~40%

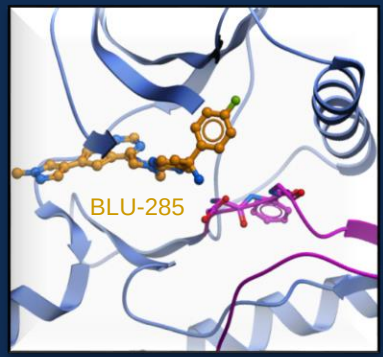
- Primary and secondary mutations cause therapeutic resistance
- Approved agents are ineffective against PDGFRα D842V

*Imatinib re-challenged

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





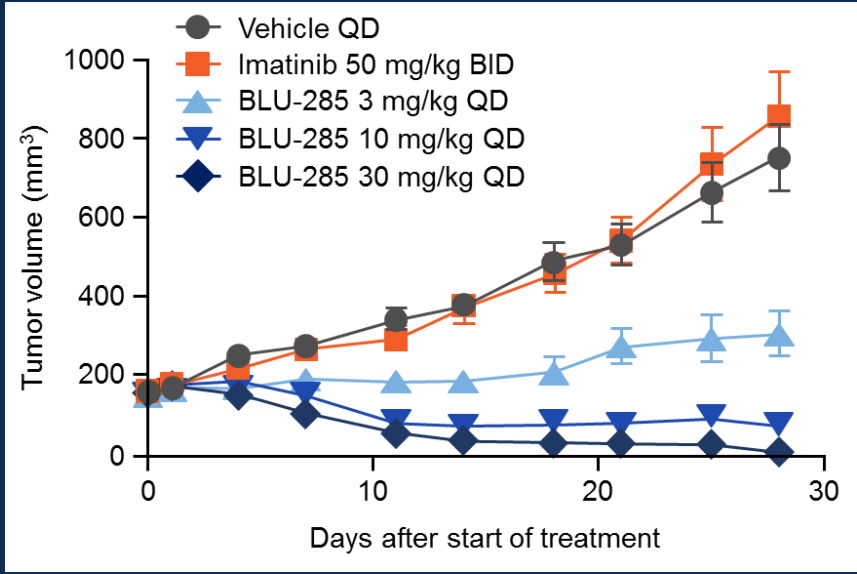


- High kinome selectivity*
- Binds active conformation

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

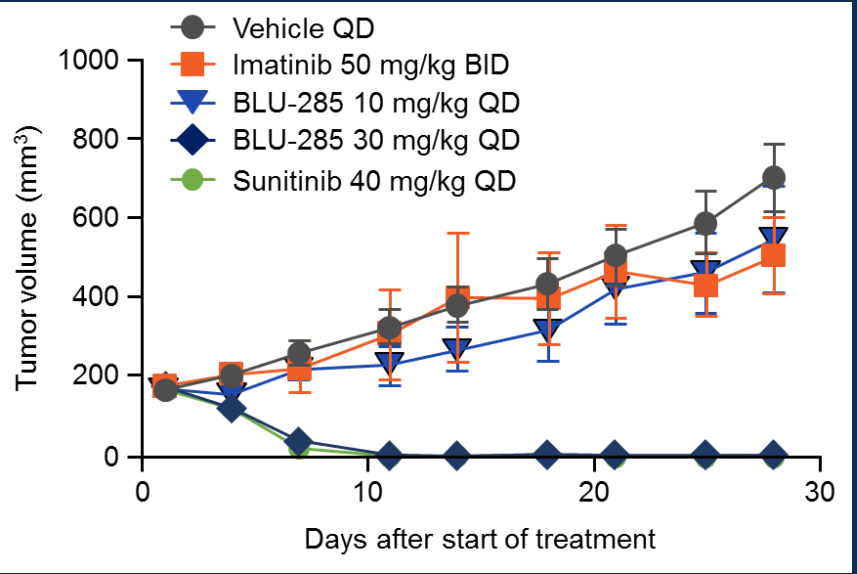
BLU-285: highly active against imatinib-resistant GIST patient derived xenografts

KIT exon 11/17 mutant



- Tumor regression at 10 and 30 mg/kg QD

KIT exon 11/13 mutant

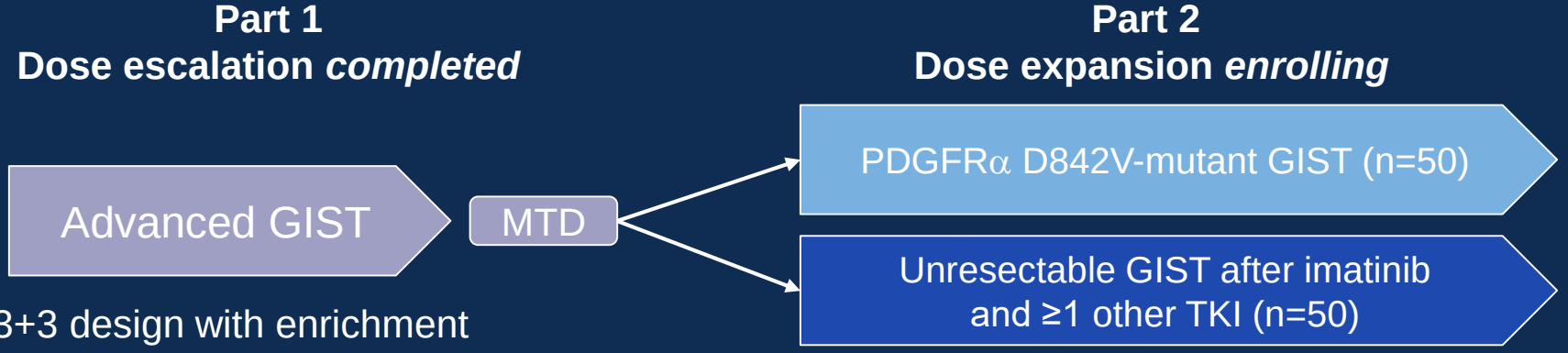


- Tumor regression at 30 mg/kg QD

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



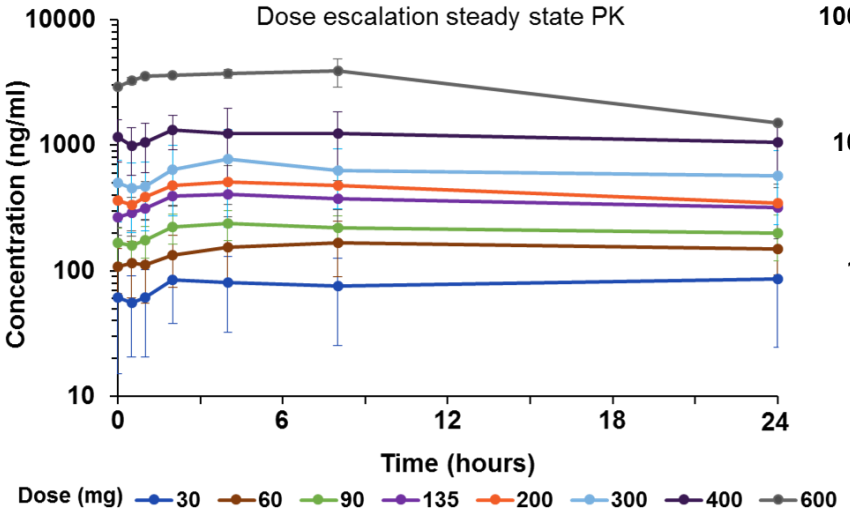
- 3+3 design with enrichment
- Dose levels: 30, 60, 90, 135, 200, 300, 400 and 600 mg QD
- MTD determined to be 400 mg PO QD

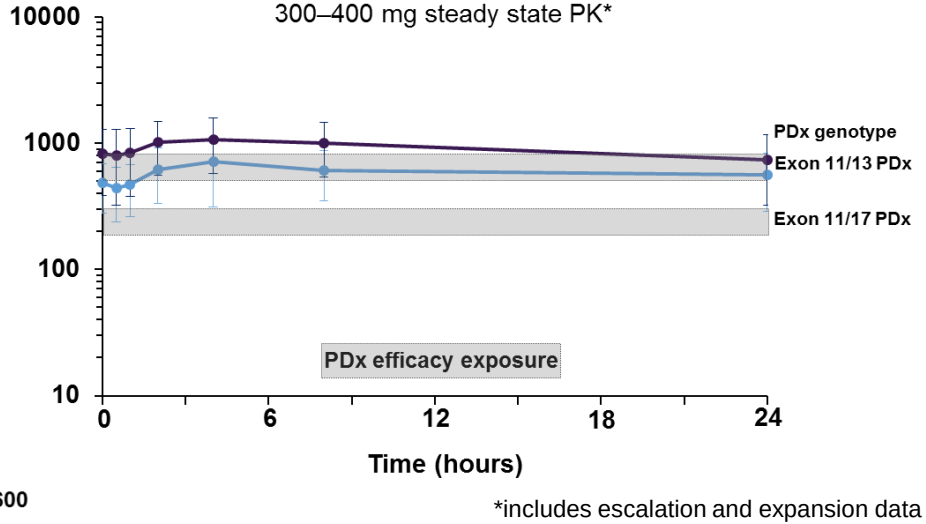
Demography and baseline patient characteristics

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



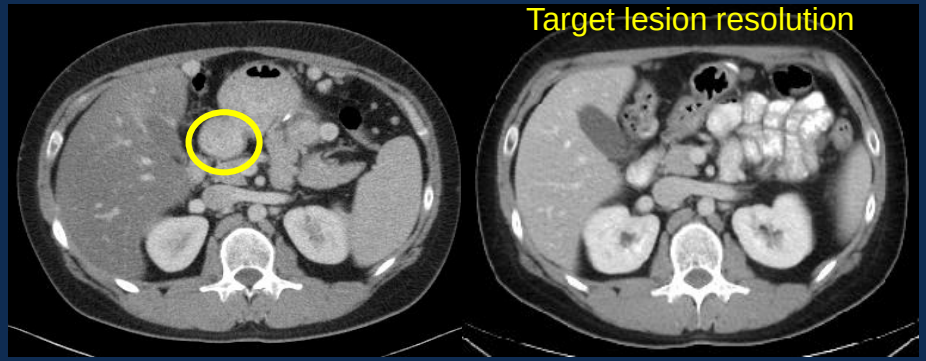


*includes escalation and expansion data

- 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

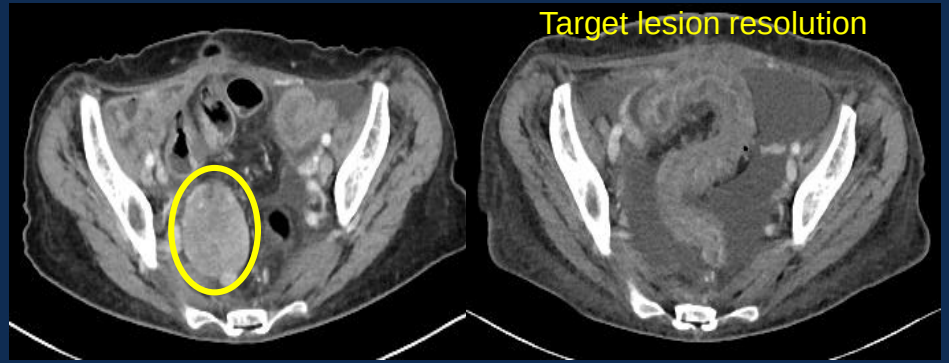
BLU-285 300 mg (dose escalation)



Baseline | After 4 months

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

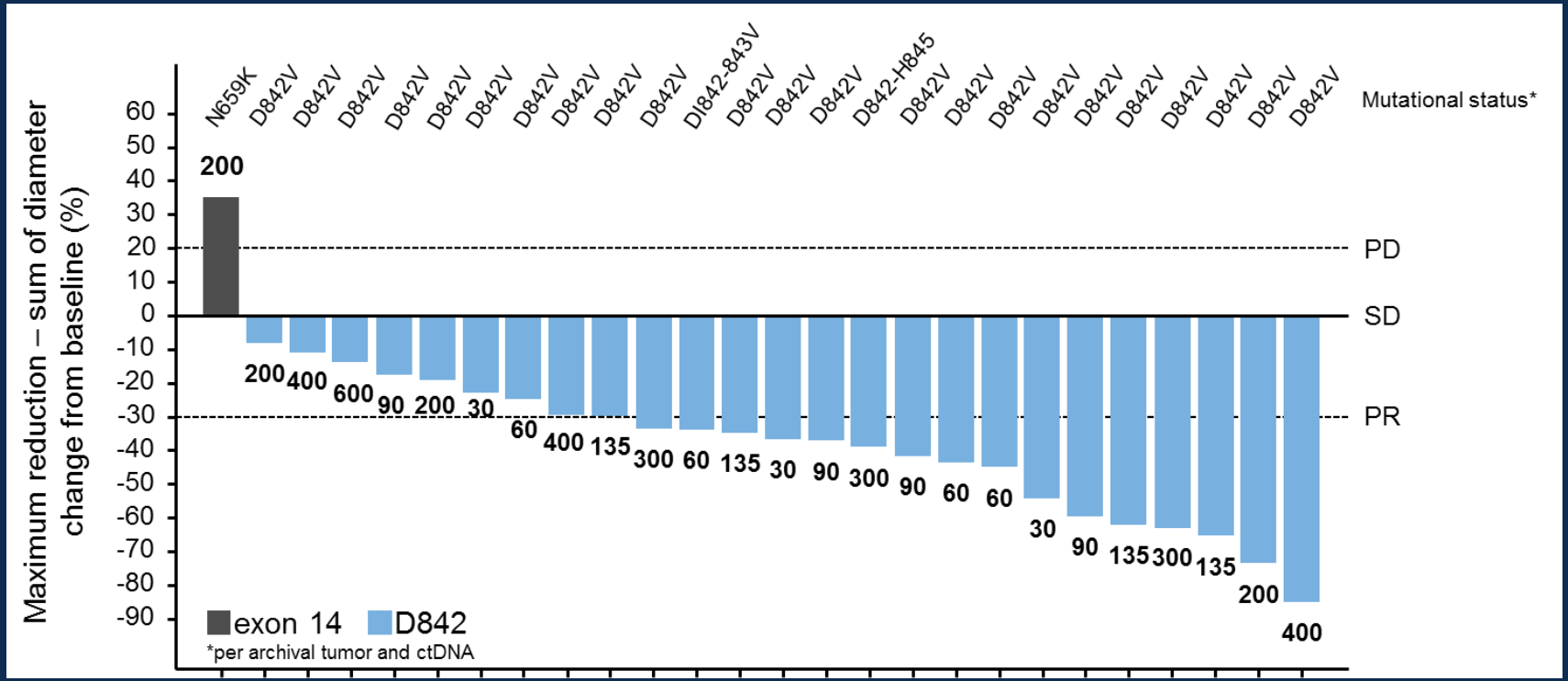
BLU-285 400 mg (dose expansion)



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)



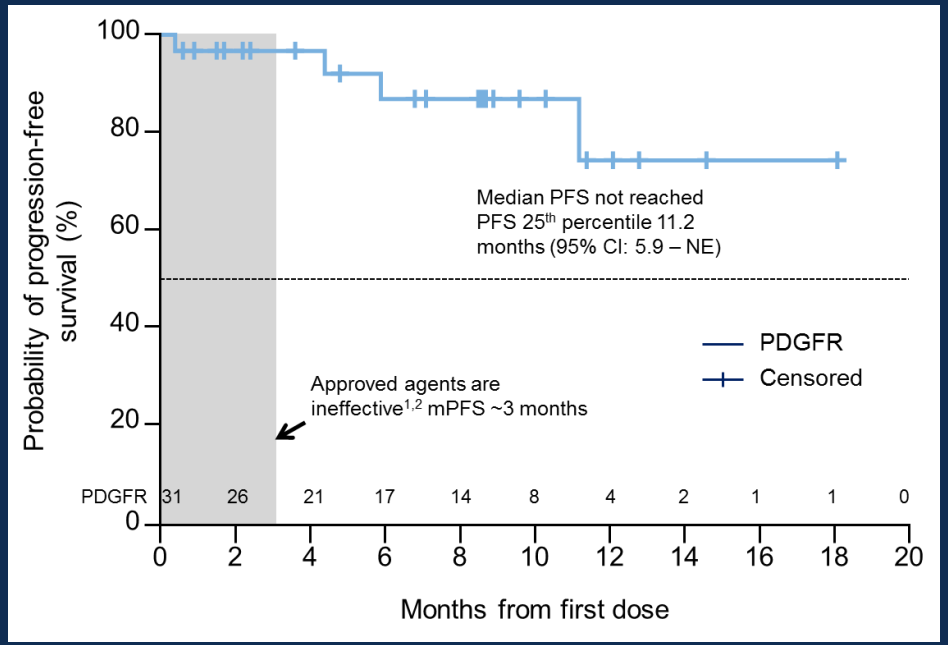
High response rate and prolonged PFS in PDGFRα D842-mutant GIST

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

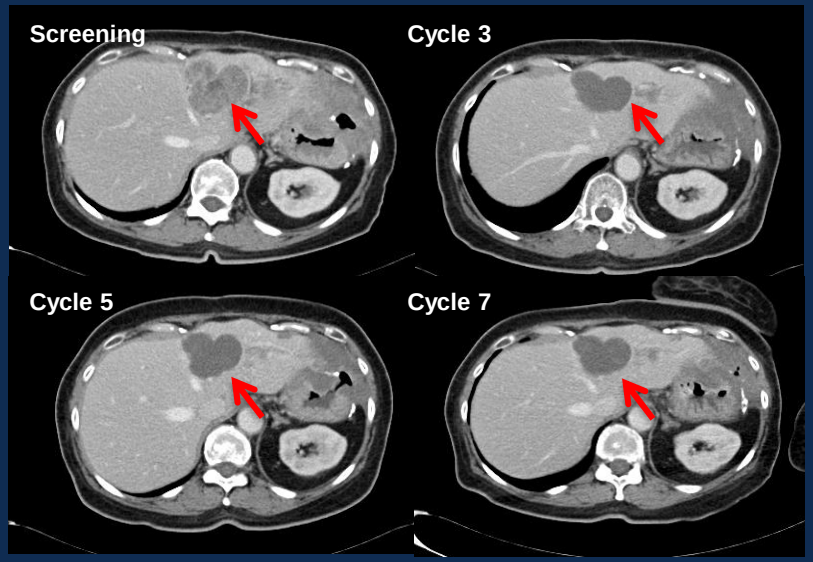
* 12 confirmed, 3 pending confirmation

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



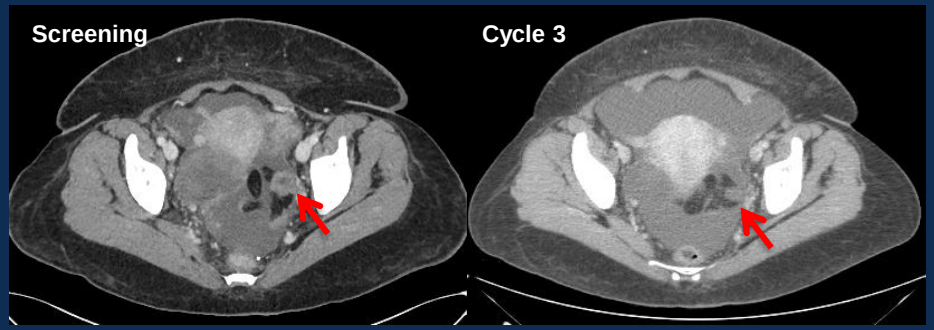
Radiographic response in heavily pre-treated KIT-mutant GIST

BLU-285 300 mg (dose escalation)



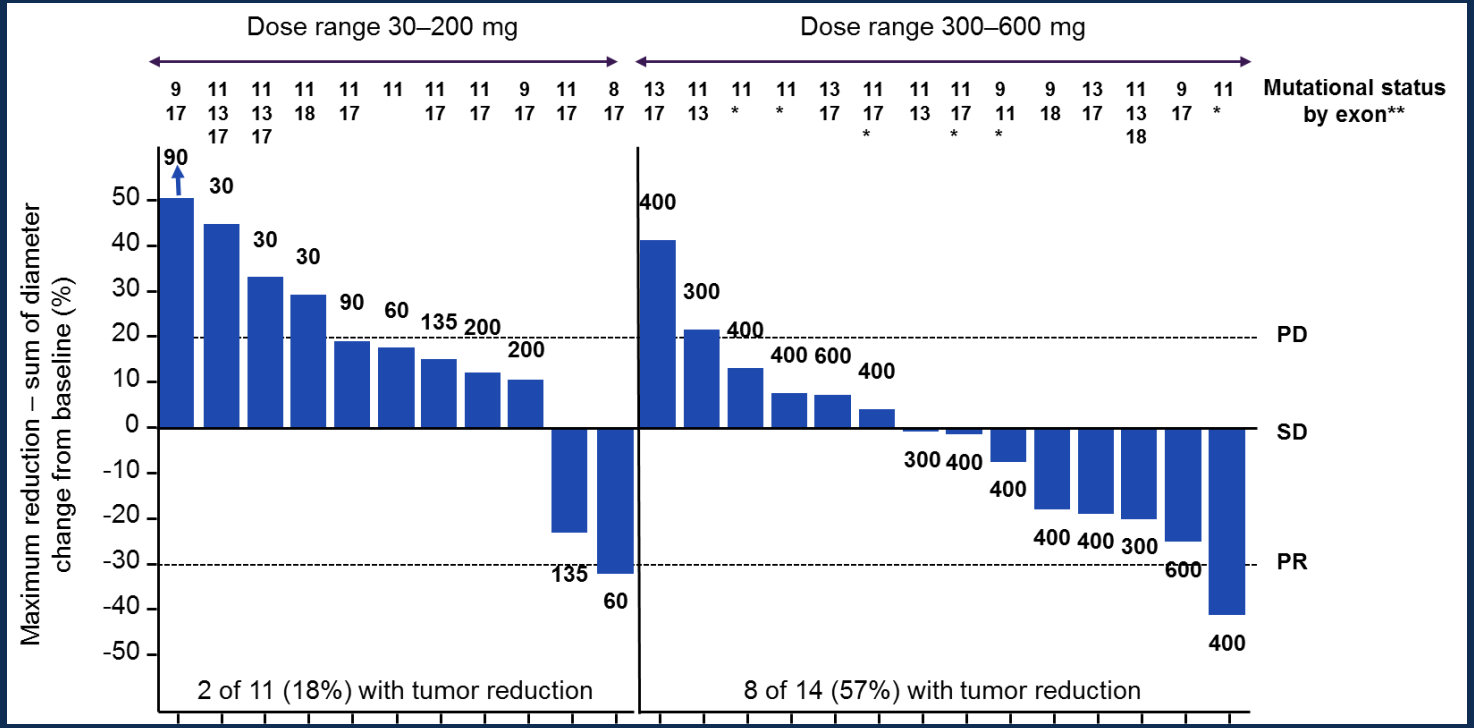
- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI PR (density -53%); RECIST SD (-21%)

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

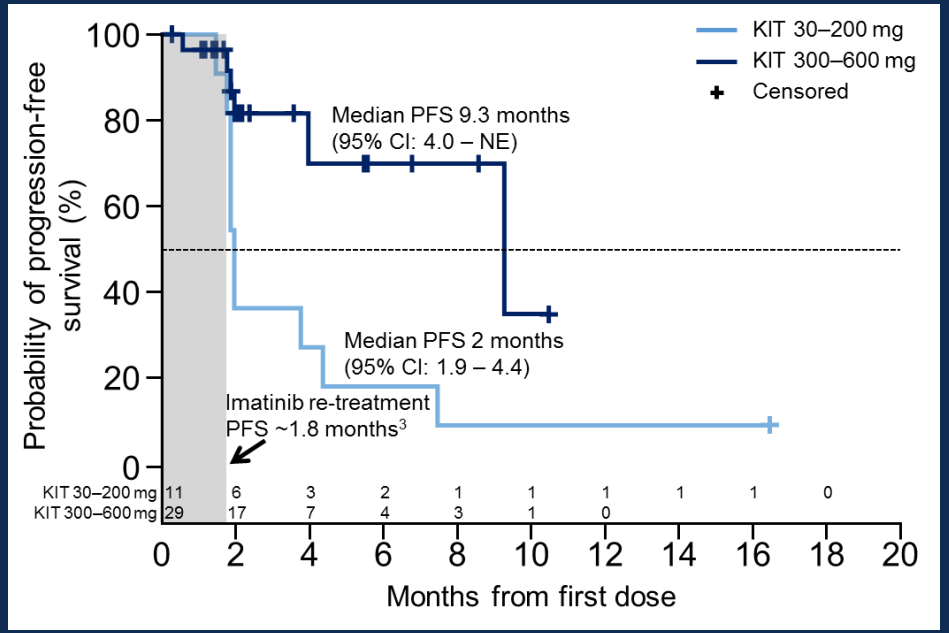
Central radiographic review

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

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- 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

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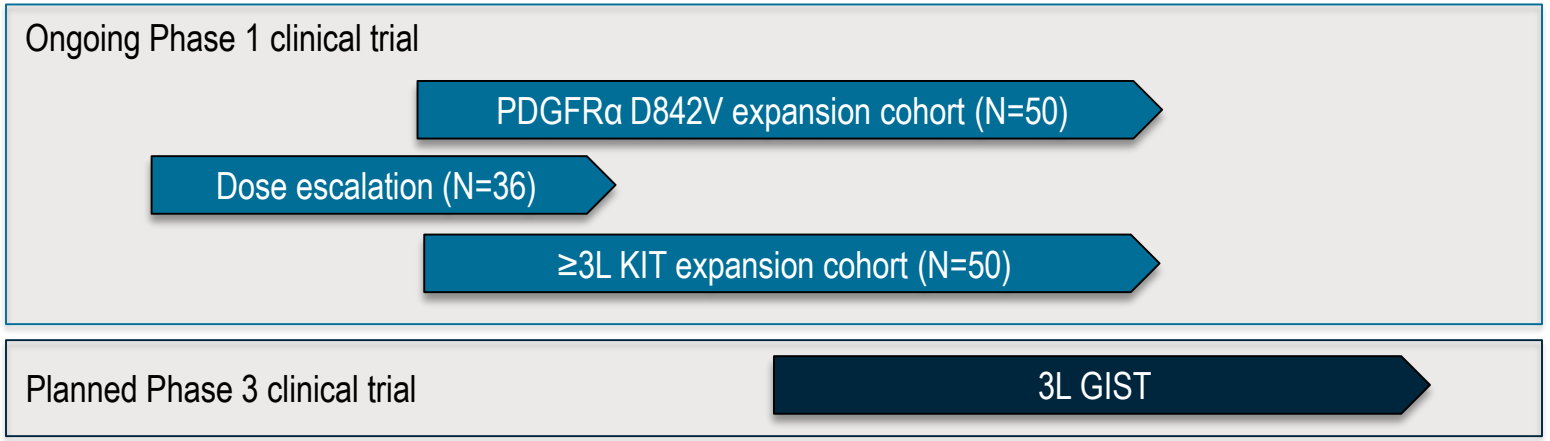
Proposed registration path

Andy Boral, M.D.
Chief Medical Officer

BLU-285 clinical development program in advanced GIST



Breakthrough Therapy Designation granted for treatment of patients with unresectable or metastatic GIST harboring the PDGFRα D842V mutation

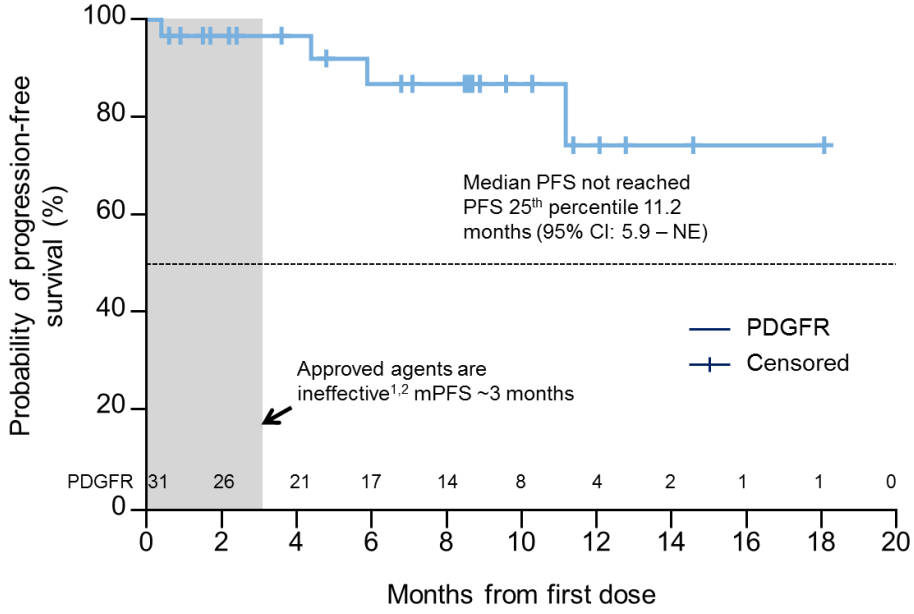
Strong clinical activity in PDGFRα D842V-driven GIST supports expedited approach to clinical development

Central Radiographic Review

Best Response	Choi Criteria (N = 25)	mRECIST 1.1 (N = 25)
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**
  - ORR ~ 0%



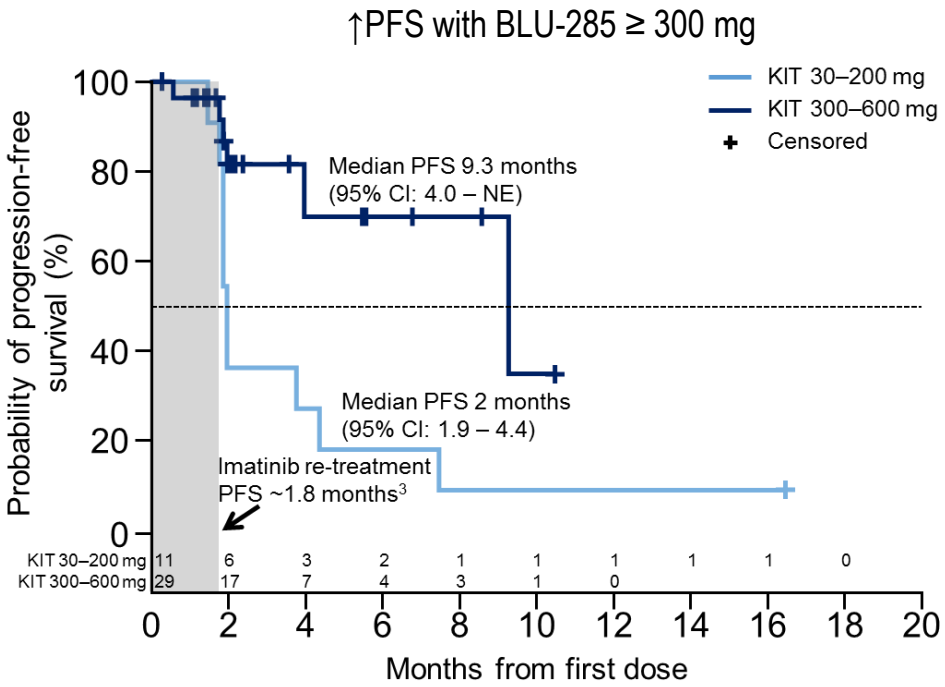
9-month PFS is estimated at 87%

**Cassier CCR (2012); Yoo Can Res Treat (2015).

Preliminary FDA feedback supports potentially expedited approval path for BLU-285 in PDGFRα D842V-driven GIST

- Breakthrough Therapy Designation granted for treatment of patients with unresectable or metastatic GIST harboring the PDGFRα D842V mutation
- FDA is open to considering additional data from ongoing Phase 1 trial as basis for New Drug Application in PDGFRα D842V-driven GIST
- Phase 1 trial accrual continues with 32 PDGFRα-driven GIST patients enrolled as of April 28, 2017 including 12 at 300-400 mg QD dose levels
    - Estimate expansion cohort enrollment complete by mid-year 2018

Prolonged progression free survival demonstrated in 5L KIT-driven GIST



Prior kinase inhibitor treatment

- Median of 4 therapies
- 90% had ≥3 therapies
- 85% had regorafenib

Regorafenib PFS in 3L

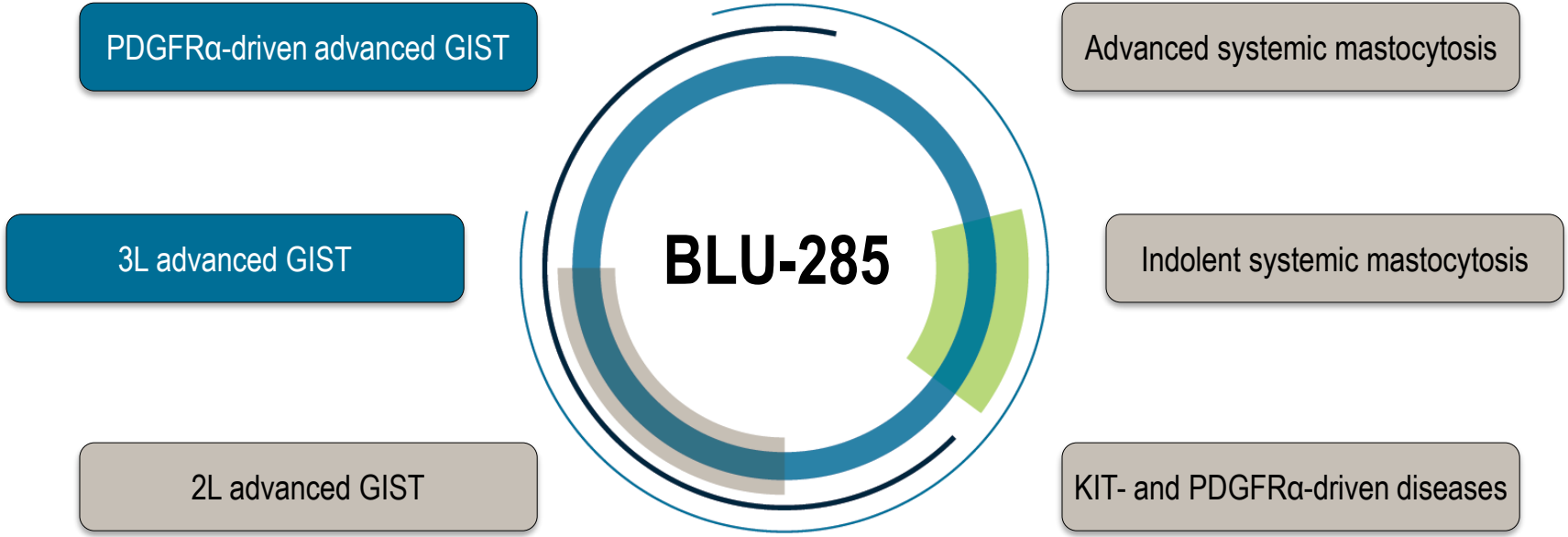
- ~4.8 months

Stable disease is clinically important to patients and physicians

Encouraging clinical activity supports advancing clinical development of BLU-285 into earlier lines of treatment

- Potential Phase 3 trial design:
  - Population: 3L GIST
  - Comparator: regorafenib, with option to cross-over to BLU-285
  - Primary endpoint: PFS
  - Trial sites: global
- Investigators and expert advisors are enthusiastic for 3L approach
- Interactions with global regulatory authorities planned
- Trial initiation planned in 1H 2018

Progress in advanced GIST represents a foundation for a broader vision



Question & Answer Session

Closing Remarks

Jeff Albers

Chief Executive Officer

Robust pipeline of diverse clinical stage assets

DRUG CANDIDATE	DISCOVERY	PRECLINICAL	CLINICAL	COMMERCIAL RIGHTS
BLU-285 Inhibitor of KIT, including exon 17 mutations, and PDGFRα, including the D842V mutation			PHASE 1 - PDGFRα-DRIVEN GIST PHASE 1 - KIT-DRIVEN GIST PHASE 1 – SYSTEMIC MASTOCYTOSIS	
BLU-554 Inhibitor of FGFR4			PHASE 1 – HEPATOCELLULAR CARCINOMA	
BLU-667 Inhibitor of RET fusions, mutations and resistant mutants			PHASE 1 – NSCLC & THYROID*	
PRKACA Inhibitor of PRKACA fusions			FLC	
Cancer immunotherapy Immunokinases			UP TO 5 PROGRAMS, STAGE UNDISCLOSED**	Roche
Rare genetic disease			TARGET AND DEVELOPMENT STAGE UNDISCLOSED	ALEXION

FLC, Fibrolamellar carcinoma; GIST, advanced gastrointestinal stromal tumors; NSCLC, non-small cell lung cancer. All Phase 1 clinical trials are in advanced disease.
*Phase 1 trial includes a basket cohort that consists of other advanced solid tumors with RET alterations.
**Blueprint Medicines has U.S. commercial rights for up to two programs. Roche has worldwide commercialization rights for up to three programs and ex-U.S. commercialization rights for up to two programs.

With maturing datasets, additional clinical data updates for BLU-285 and BLU-554 are expected in 2H 2017

	BLU-285 in systemic mastocytosis	BLU-554 in hepatocellular carcinoma
Opportunity	• Poor prognosis and limited effective treatments • KIT D816V mutation is a key driver in 90-95% • ~4.1k advanced SM patients with KIT D816V mutation in major markets*	• 700k new cases and 600k deaths annually • Abnormally activated FGFR4 pathway in ~30% of HCC patients • ~26.9k FGFR4+ HCC patients in major markets*
Previously presented Phase 1 data**	• Encouraging clinical activity, including at lower dose levels • Marked decreases in mast cell burden and improved patient symptoms • Well tolerated to date; dose escalation ongoing	• Evidence of increased clinical activity in biomarker-selected population • Well tolerated at doses up to 600 mg QD; dose expansion ongoing

*Estimated prevalence for advanced SM in major markets (US, EU5 and Japan). Estimated incidence for 1L and 2L FGFR4+ HCC in major markets.
**SM data previously presented in December 2016 at the American Society of Hematology Annual Meeting. HCC data previously presented in December 2016 at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium.

Thank you