

# Treatment of Imatinib-resistant GIST: The Next Generation

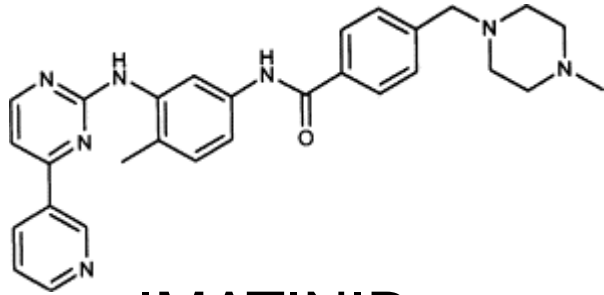


Dr. Michael Heinrich, M.D  
OHSU Knight Cancer Institute  
Portland, OR

# Background

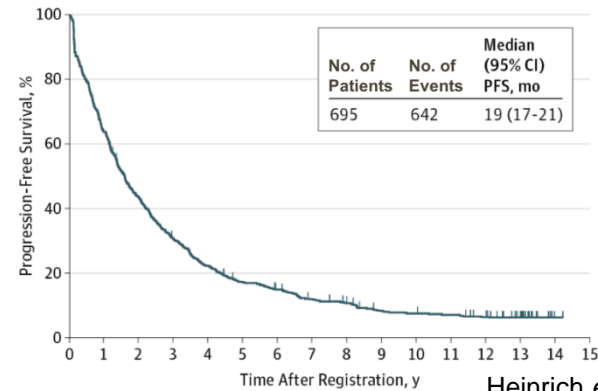
- Small molecule kinase inhibitors of KIT/PDGFRα such as imatinib and sunitinib have transformed the medical treatment of advanced GIST
- However, disease control in the metastatic setting is limited by the development of drug-resistant clones
- Drug-resistance is commonly due to the development of acquired mutations in the disease causing mutant kinase (e.g. KIT)
- To date, all approved TKIs used for the treatment of GIST are competitive ATP inhibitors and bind to the inactive kinase structure

# First line:



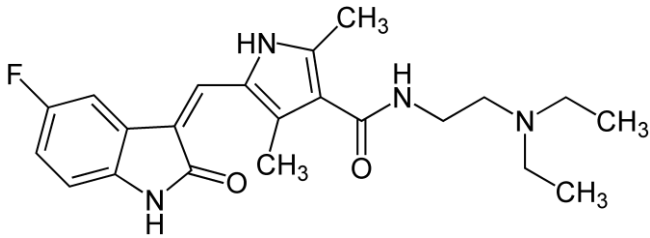
IMATINIB

**B** Progression-free survival

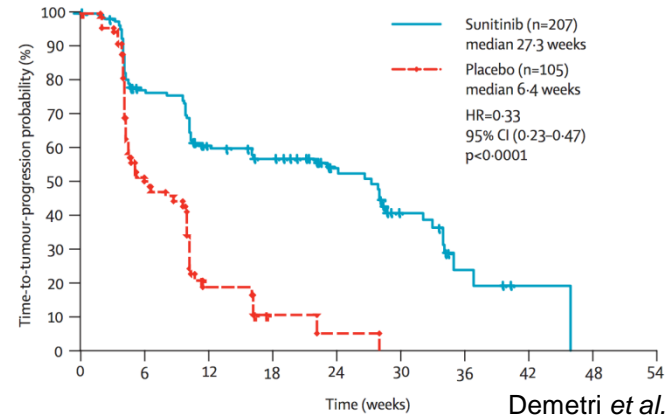


Heinrich *et al.* JAMA (2017)

# Second line:

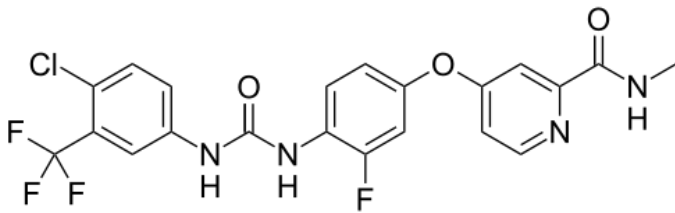


SUNITINIB



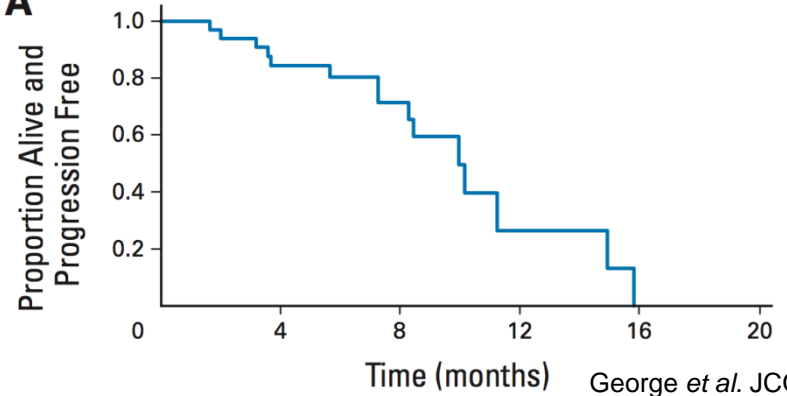
Demetri *et al.* Lancet (2006)

# Third line:



REGORAFENIB

**A**



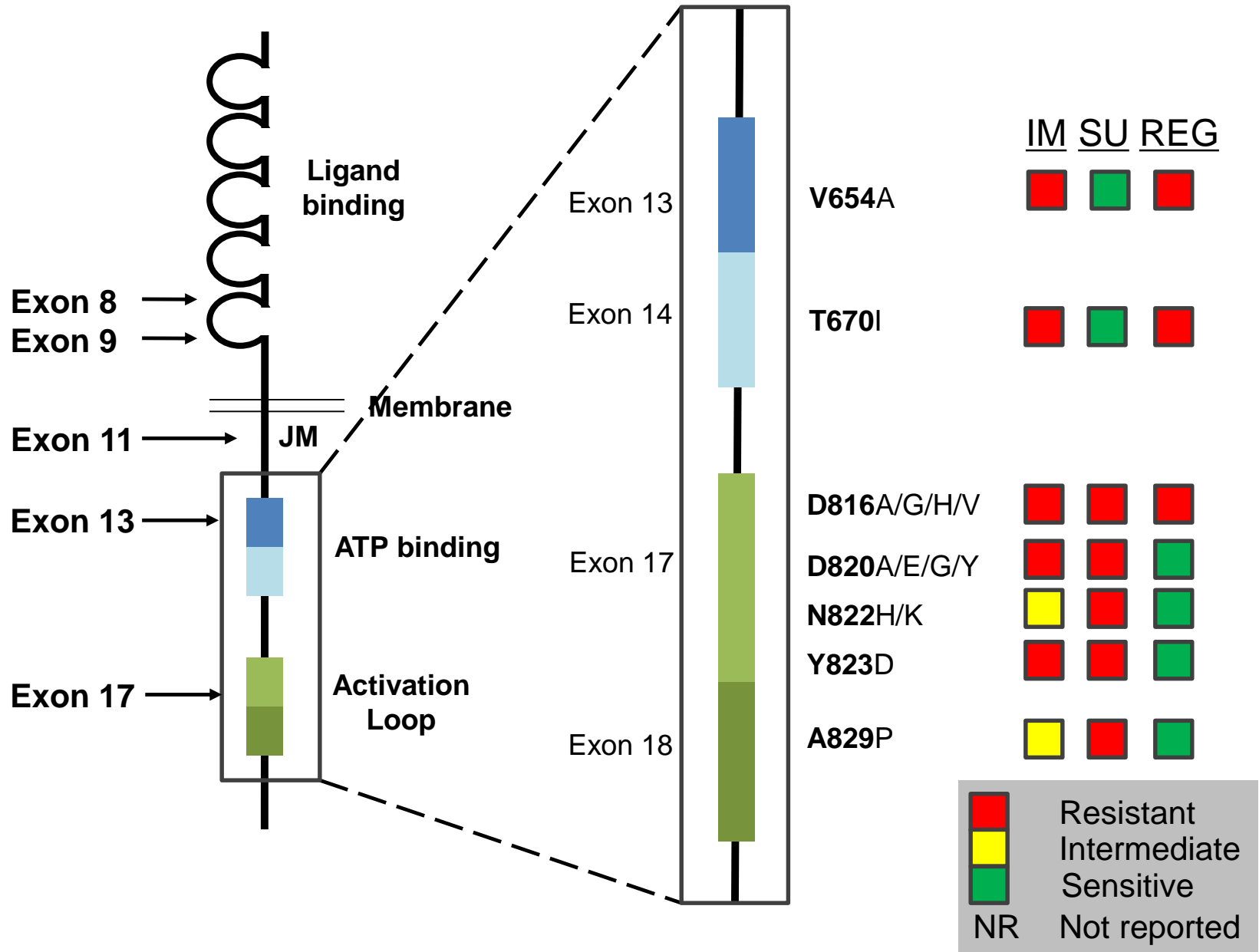
George *et al.* JCO (2012)

Primary Mutations

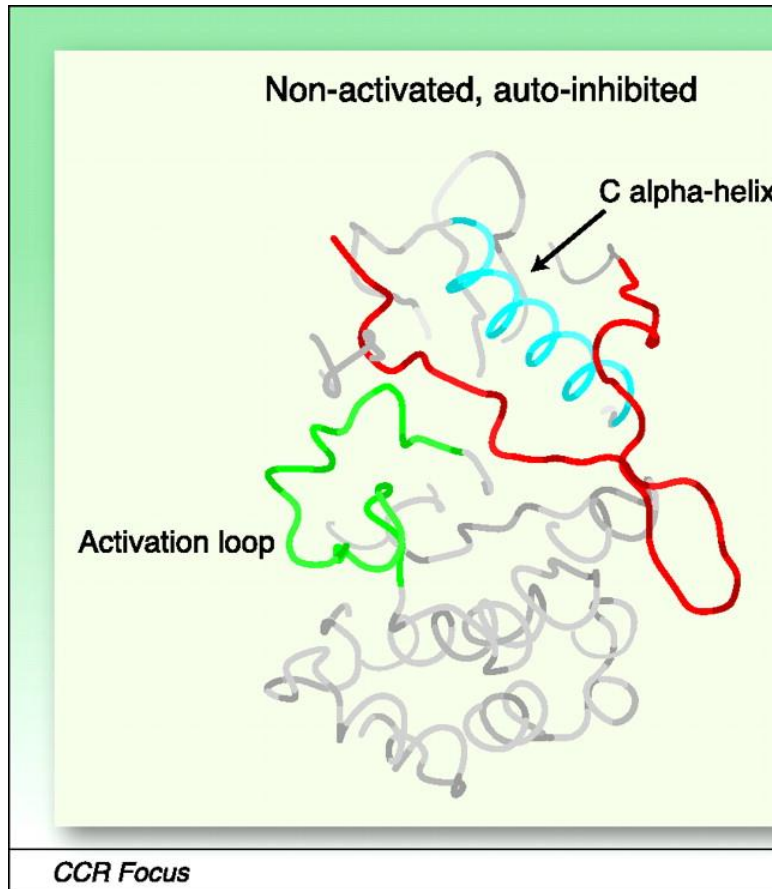
Protein Domains

Secondary Mutations

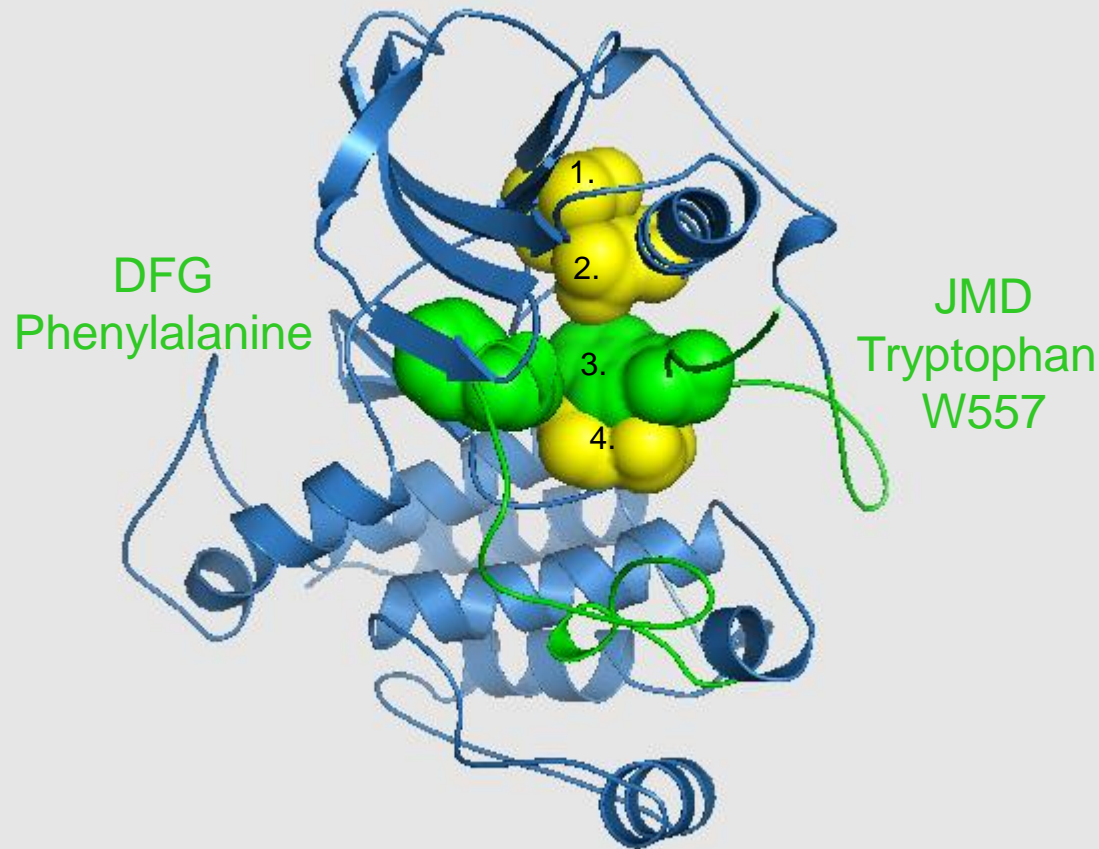
Drug Sensitivity



# Structural Regulation of KIT Enzymatic Activity



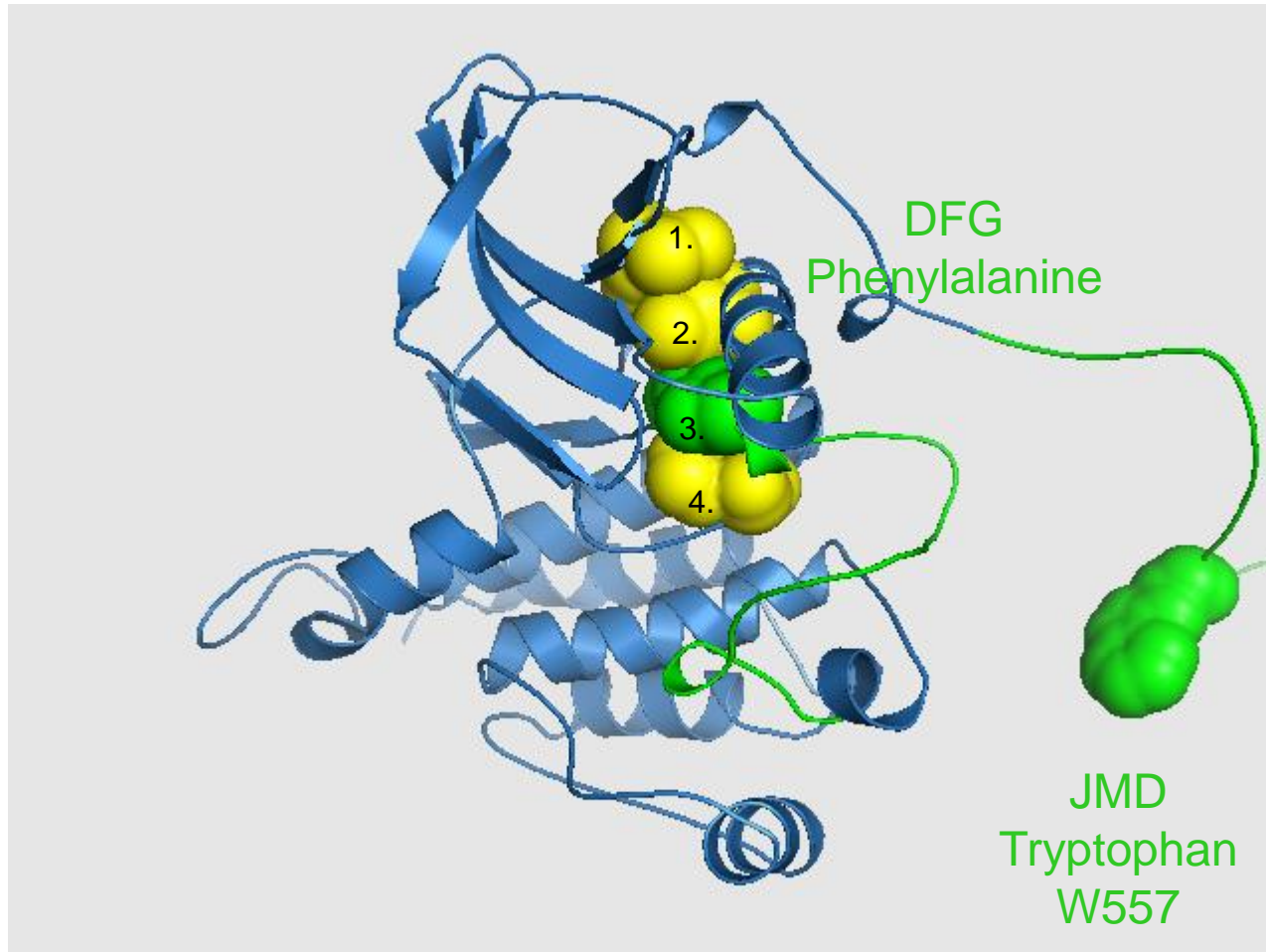
# JM-Inhibited Inactive Kinase



Snapshot 1. The rightmost green residue from the inhibitory JMD switch occupies the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this conformation, KIT kinase is in its OFF state. Note that the 'DFG' phenylalanine amino acid (green) is in the left-most position, blocking the ATP pocket.

# Activated Kinase Structure

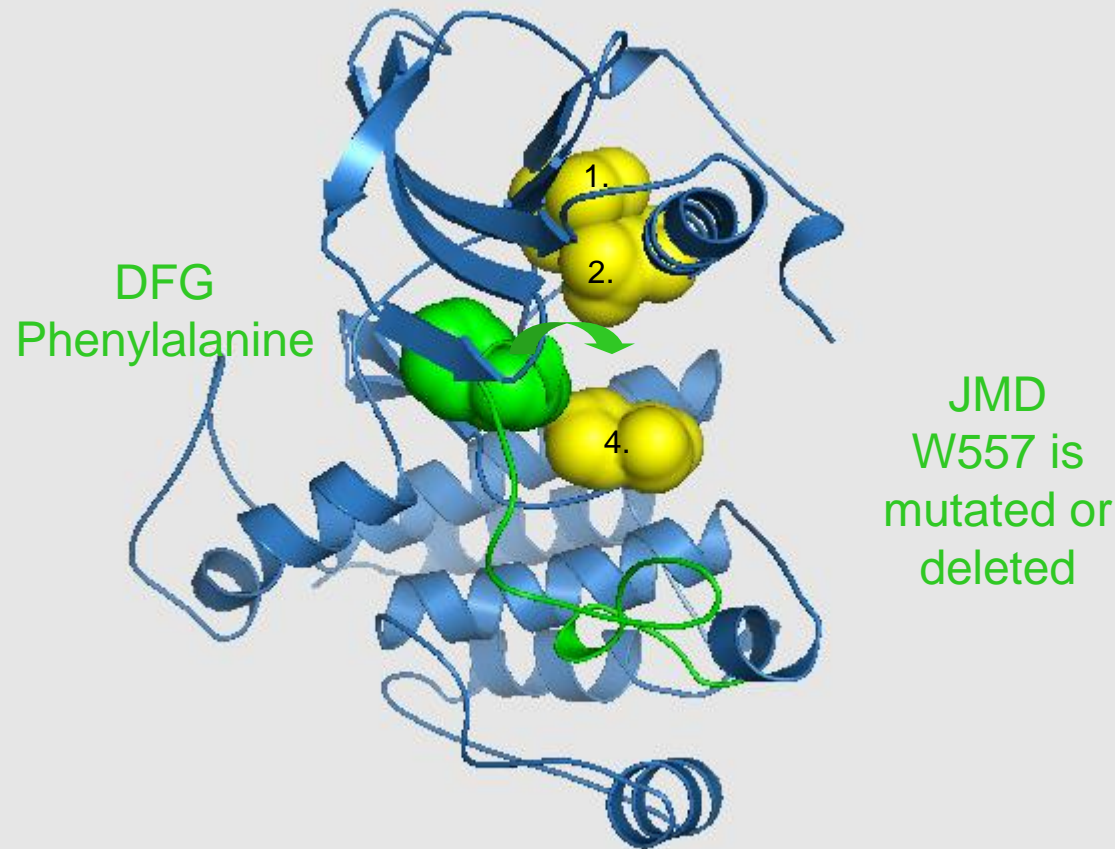


Snapshot 2. The rightmost green residue from the inhibitory JMD switch has been moved out of the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this conformation, KIT kinase is in its ON state. Note that the 'DFG' phenylalanine amino acid (green) is now in the #3 position in the vertical spine.



# Effect of JM-mutation on Kinase Conformation

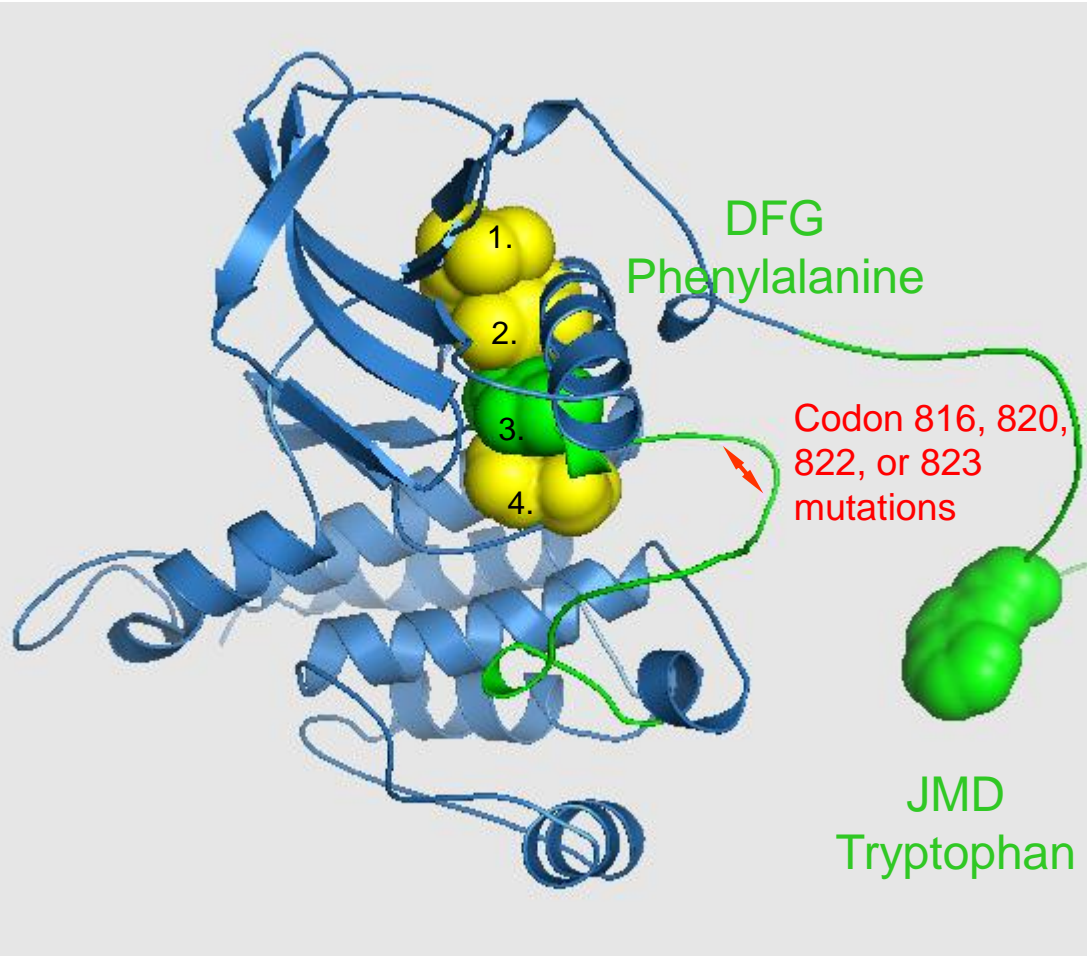


Snapshot 3. The rightmost green residue from the inhibitory JMD switch has been mutated and can no longer function as an inhibitory element to bind into the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this mutant form, the 'DFG' phenylalanine (green) is free to move over and occupy the #3 spine position and activate the kinase since the inhibitory JMD has been mutated.



# Effect of Activation Loop Mutations on Kinase Structure

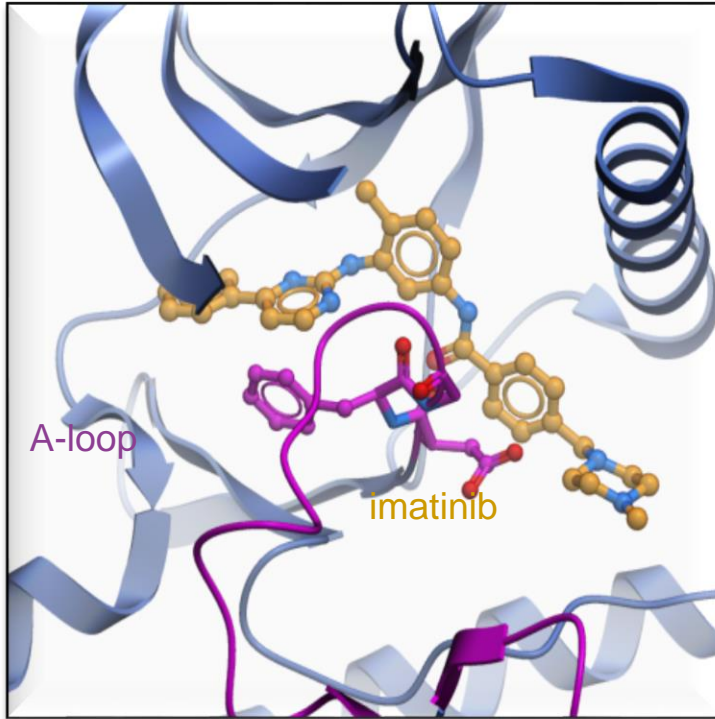


Snapshot 4. The rightmost green residue from the inhibitory JMD switch has been moved out of the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow). Mutations of the activation loop stabilize the kinase in the active conformation.

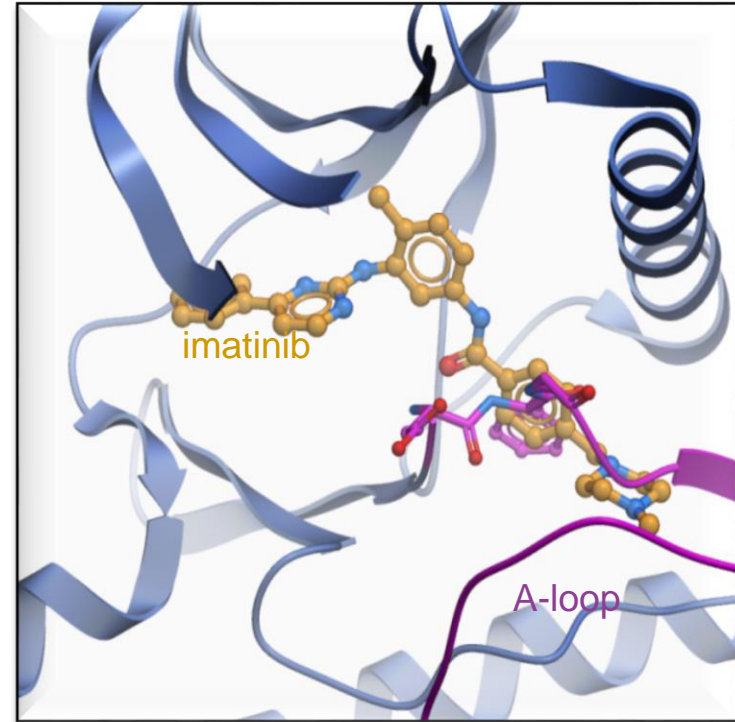
In this conformation, KIT kinase is in its ON state. Note that the 'DFG' phenylalanine amino acid (green) is now in the #3 position in the vertical spine.

# Imatinib can only bind (inhibit) the inactive form of KIT

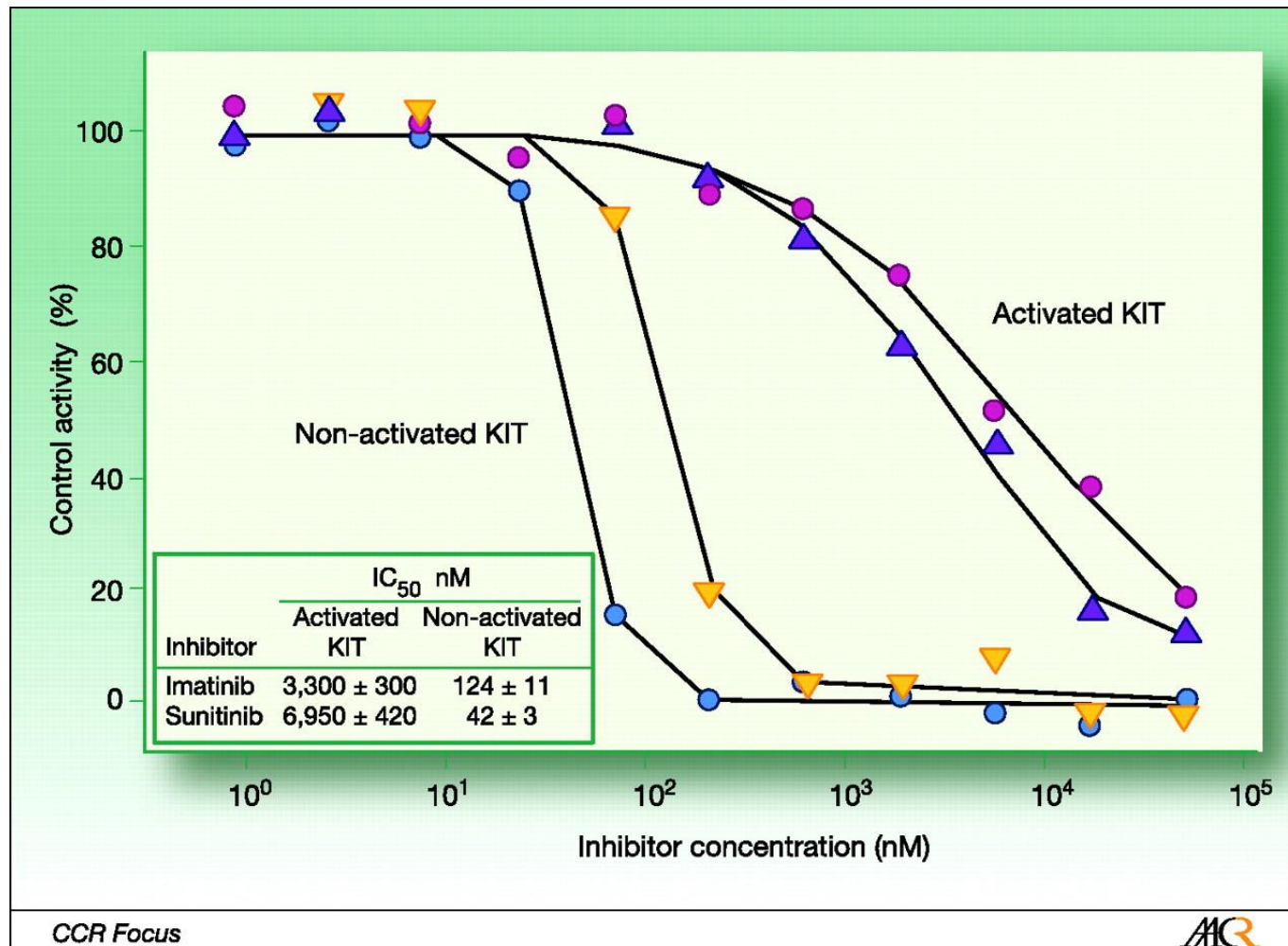
Inactive conformation



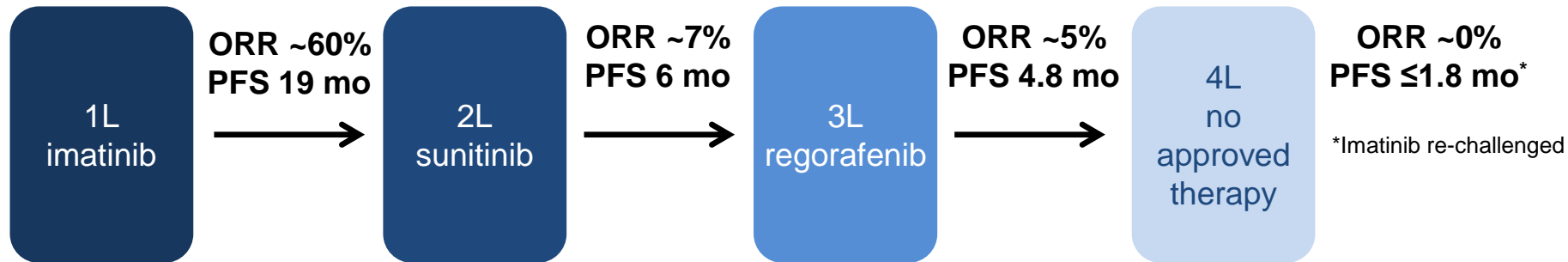
Active conformation



# Imatinib and Sunitinib (and Regorafenib) Only Inhibit the Inactive Form of KIT



# Beyond imatinib, there are no highly effective therapies



Resistance mutation	Prevalence	
	Primary	Secondary
PDGFR $\alpha$ D842V	~5–6%	Rare
KIT exon 17/18	~1%	2L ~23% ≥3L ~90%
KIT exon 13	N/A	2L ~40%

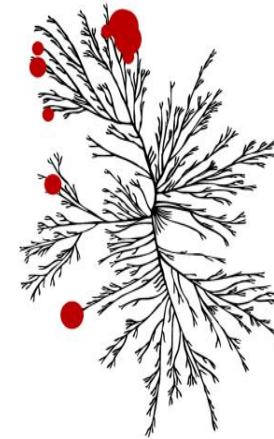
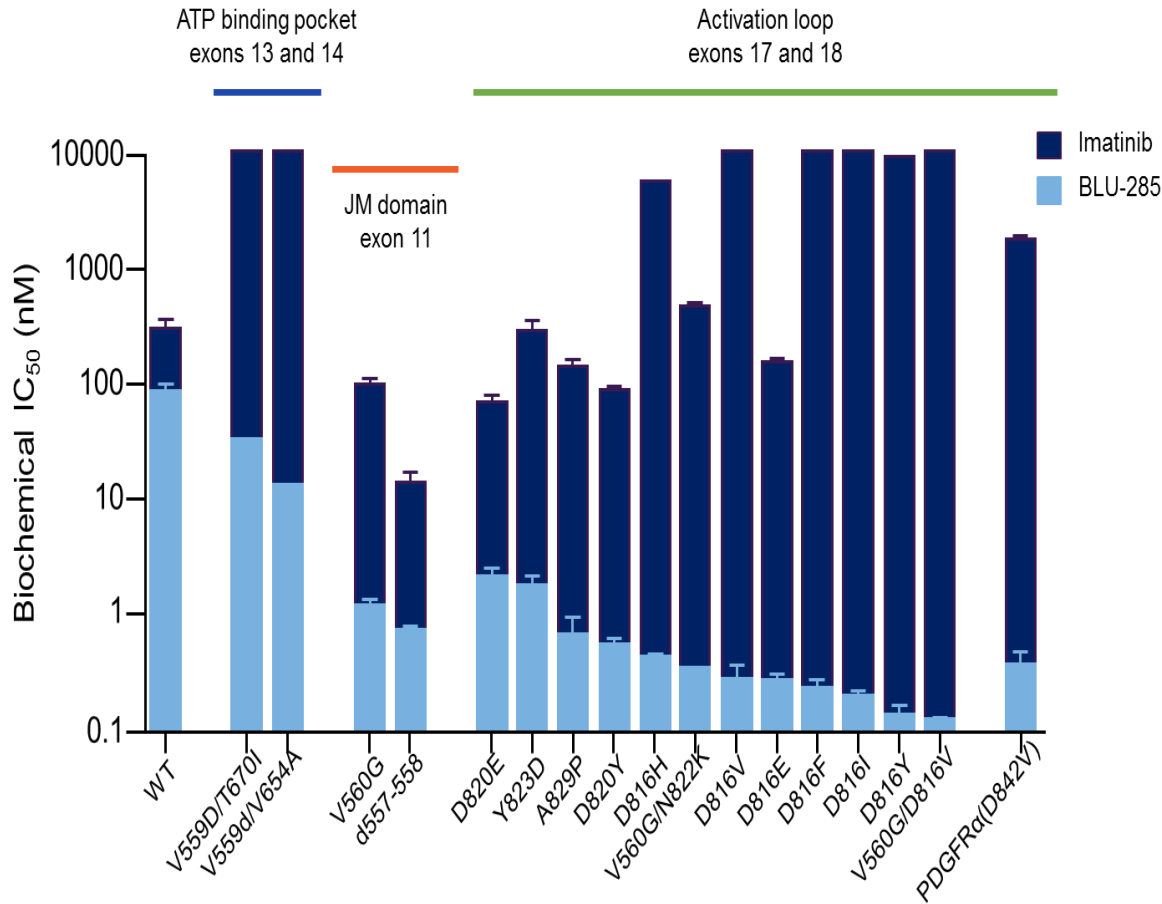
Primary and secondary mutations cause therapeutic resistance  
 Approved agents are ineffective against PDGFR $\alpha$  D842V

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

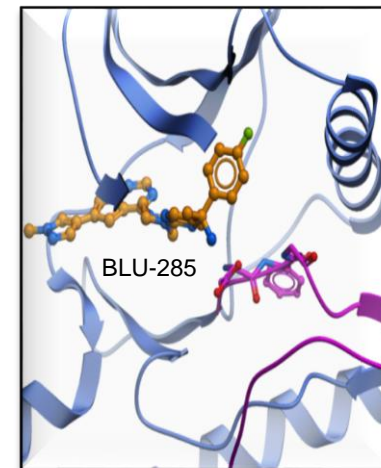
Michael Heinrich<sup>1</sup>, Robin Jones<sup>2</sup>, Margaret von Mehren<sup>3</sup>, Patrick Schoffski<sup>4</sup>, Sebastian Bauer<sup>5</sup>, Olivier Mir<sup>6</sup>, Philippe Cassier<sup>7</sup>, Ferry Eskens<sup>8</sup>, Hongliang Shi<sup>9</sup>, Terri Alvarez-Diez<sup>9</sup>, Oleg Schmidt-Kittler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

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# BLU-285: highly potent and selective targeting of KIT/PDGFR $\alpha$ mutants



- High kinase selectivity\*

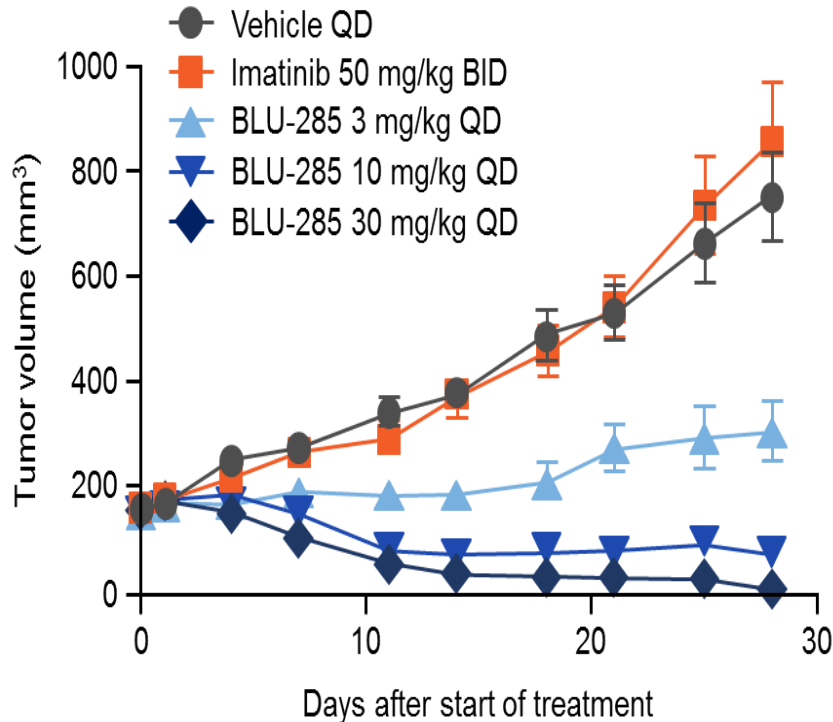


- Binds active conformation

\*Image reproduced courtesy of CSTI ([www.cellsignal.com](http://www.cellsignal.com))

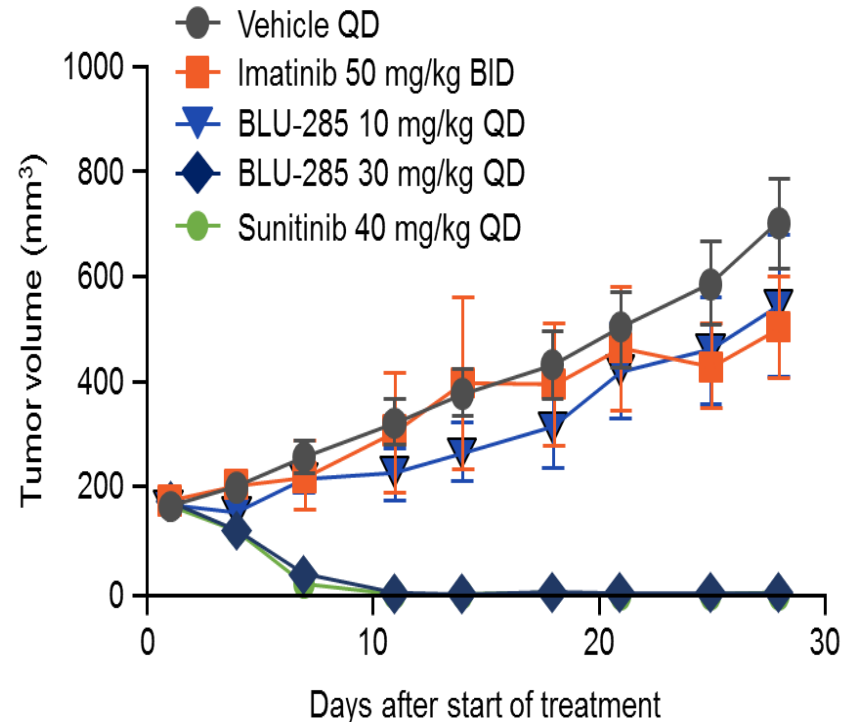
# BLU-285: highly active against imatinib-resistant GIST patient derived xenografts

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 Design

## Key objectives

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

### Part 1

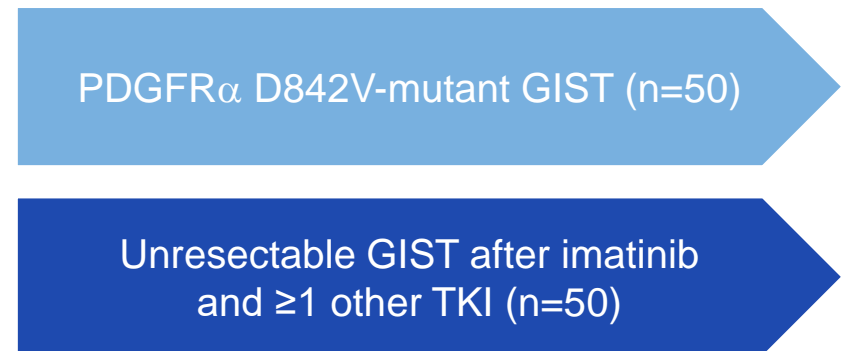
**Dose escalation *completed***



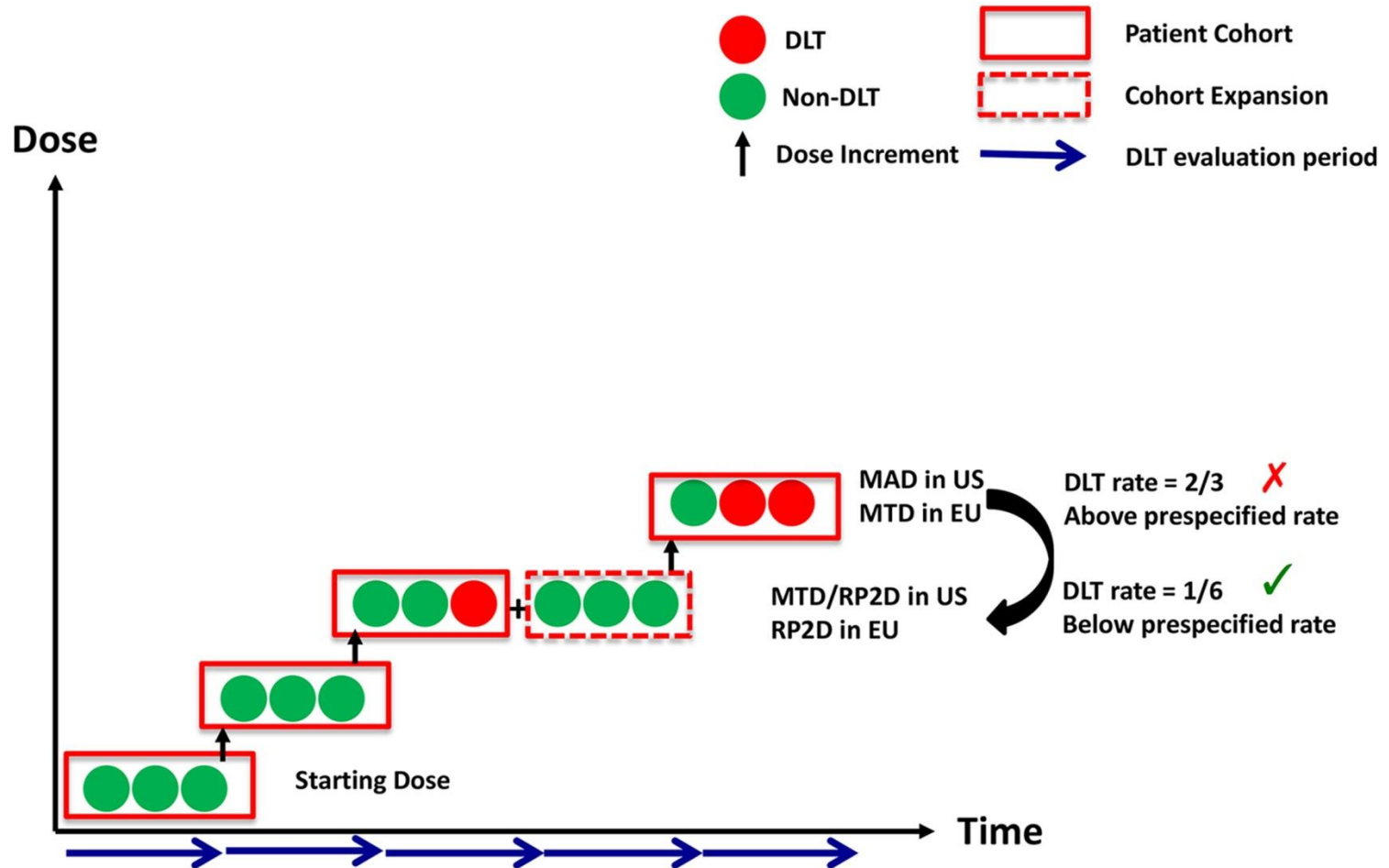
- 3+3 design with enrichment
- Dose levels: 30, 60, 90, 135, 200, 300, 400 and 600 mg QD
- MTD determined to be 400 mg PO QD

### Part 2

**Dose expansion *enrolling***



# 3+3 Dose escalation phase 1 study design

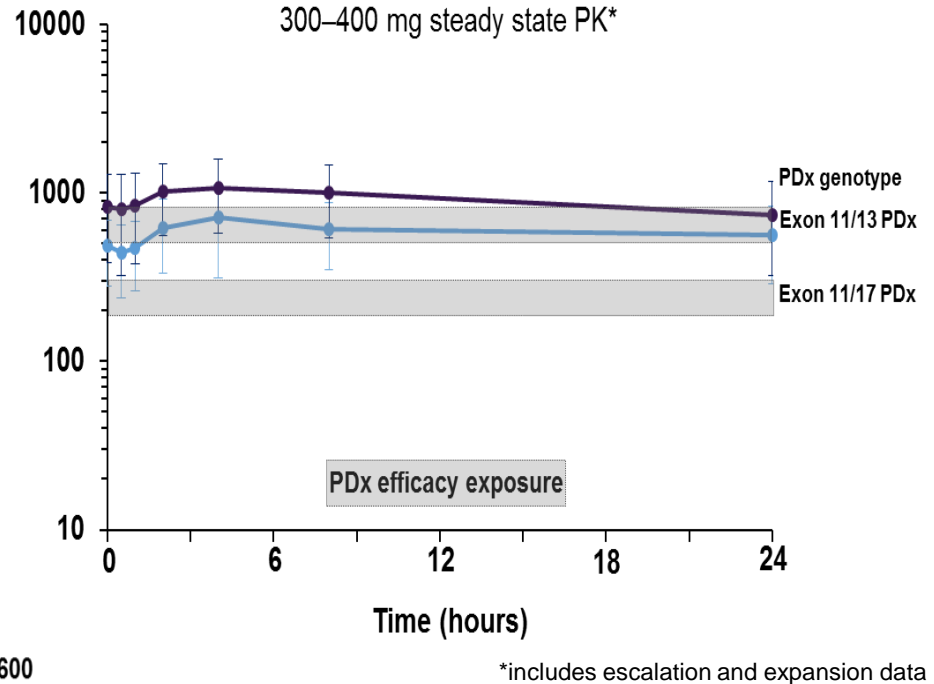
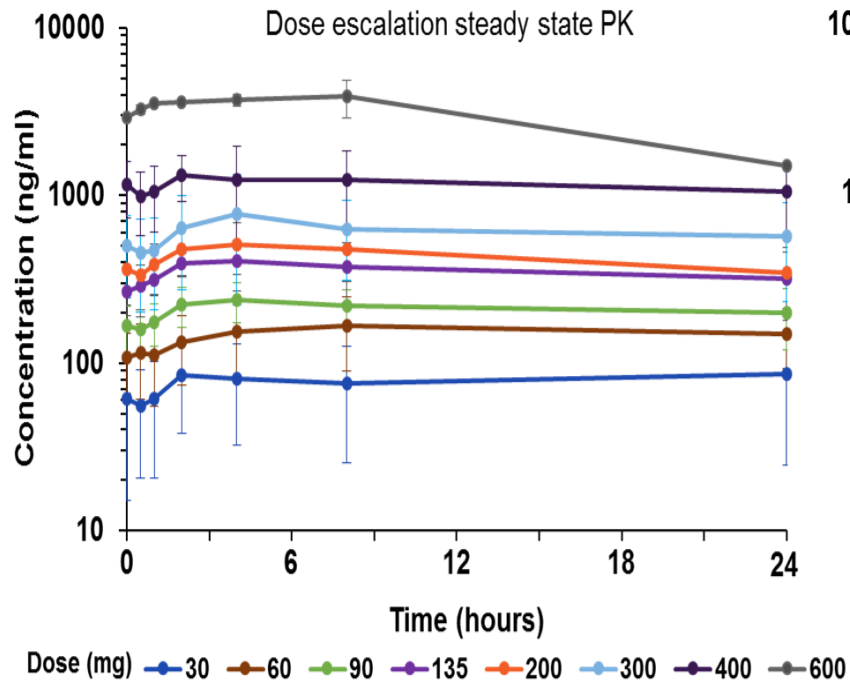


# Demography and baseline patient characteristics

Parameter	All patients, N=72	
Age (years), median (range)	61 (25–85)	
	n (%)	
GIST subtype		
KIT mutant	40 (56)	
PDGFR $\alpha$ mutant	32 (44)	
Metastatic disease	69 (96)	
Largest target lesion size (cm)		
$\leq 5$	18 (25)	
$>5$ – $\leq 10$	25 (35)	
$>10$	29 (40)	
No. prior kinase inhibitors	<u>PDGFR<math>\alpha</math></u>	<u>KIT</u>
Median (range)	1.5 (0–6)	4 (2–11)
$\geq 3$	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 once daily dosing and broad mutational coverage

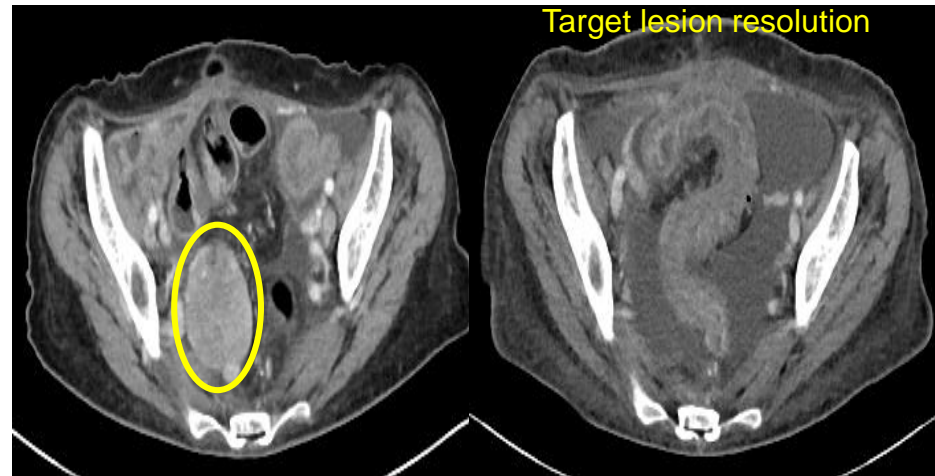


- Relatively rapid absorption  $T_{max}$  ~2–8 hours and long half-life >24 hours
- Exposure at the 300 and 400 (MTD) mg provides broad coverage of primary and secondary KIT/PDGFR $\alpha$  mutations based on patient derived xenografts (PDX)

# Radiographic response per RECIST 1.1 in PDGFR $\alpha$ D842V-mutant GIST

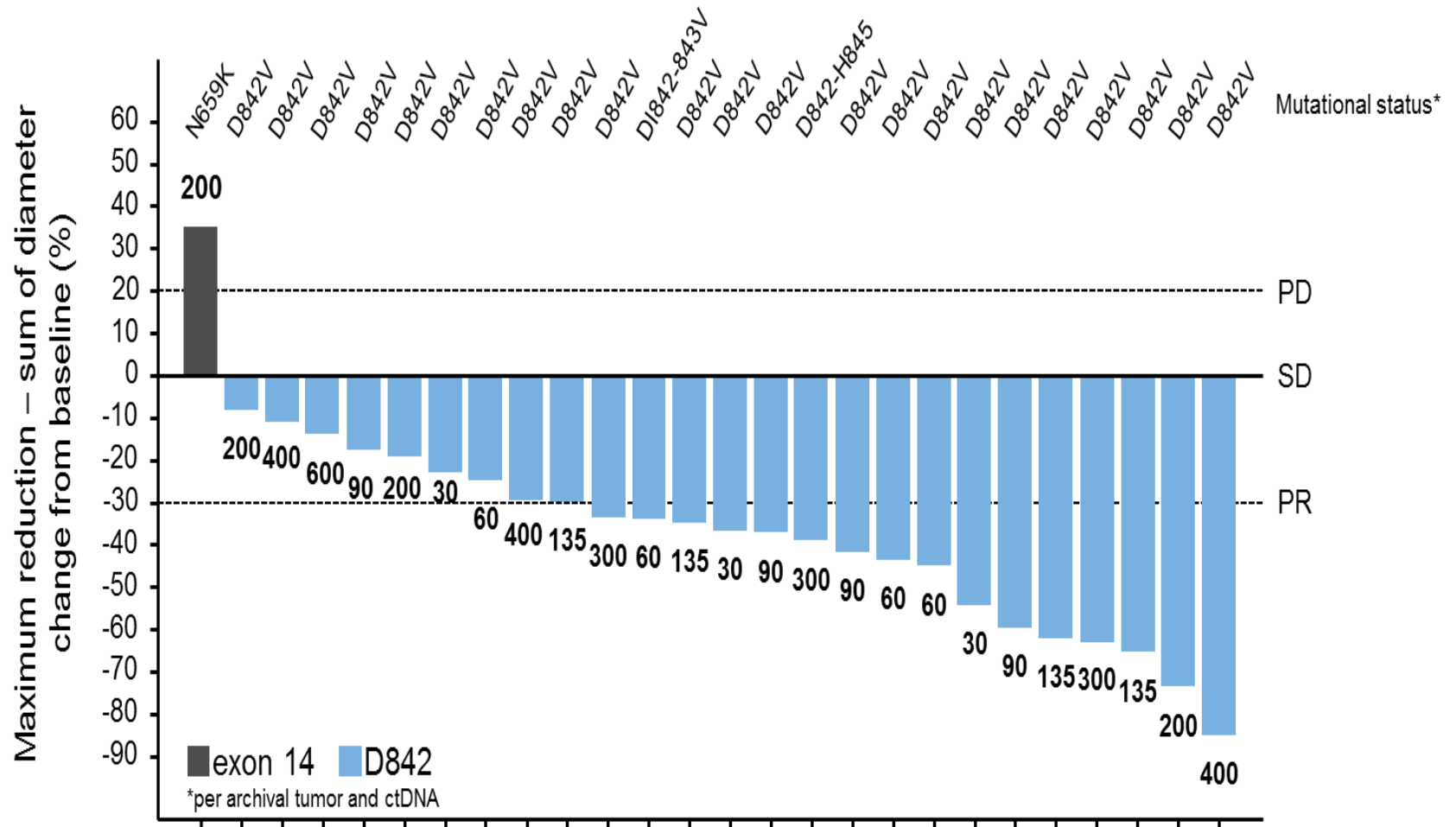


- Ongoing at cycle 5
- Prior imatinib and sunitinib
- Confirmed PR, -63% target sum



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

# Tumor regression across all dose levels in PDGFR $\alpha$ D842-mutant GIST (central radiology review)



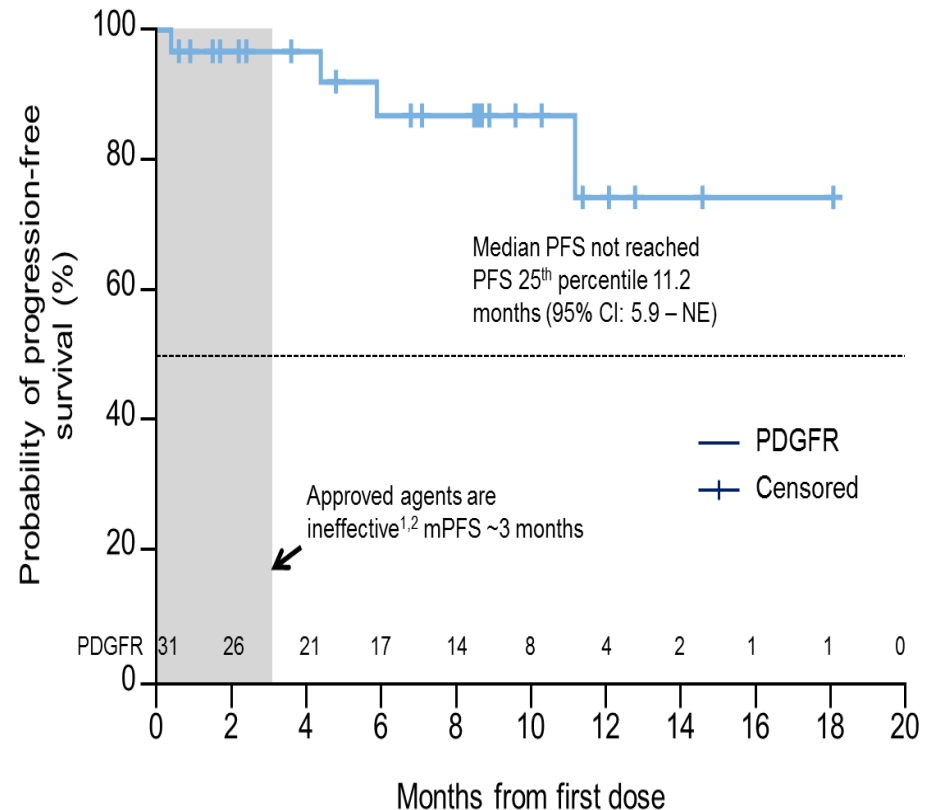
# High response rate and prolonged PFS in PDGFR $\alpha$ D842-mutant GIST

## 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

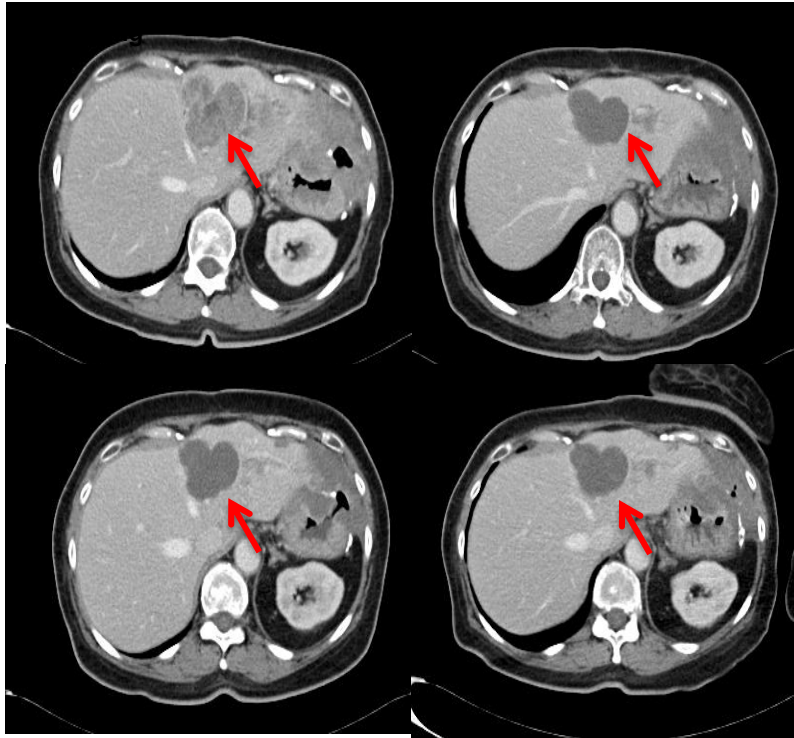
Approved agents are ineffective: ORR ~0%





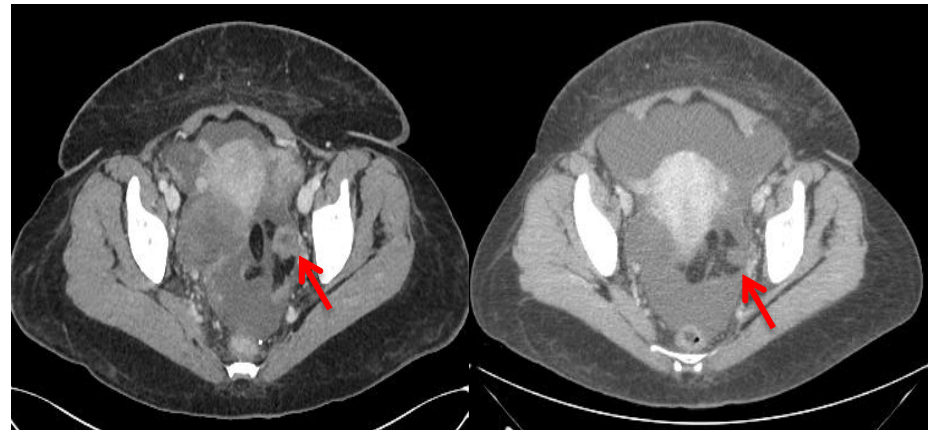
# Radiographic response in heavily pre-treated KIT-mutant GIST

BLU-285 300 mg (dose escalation)



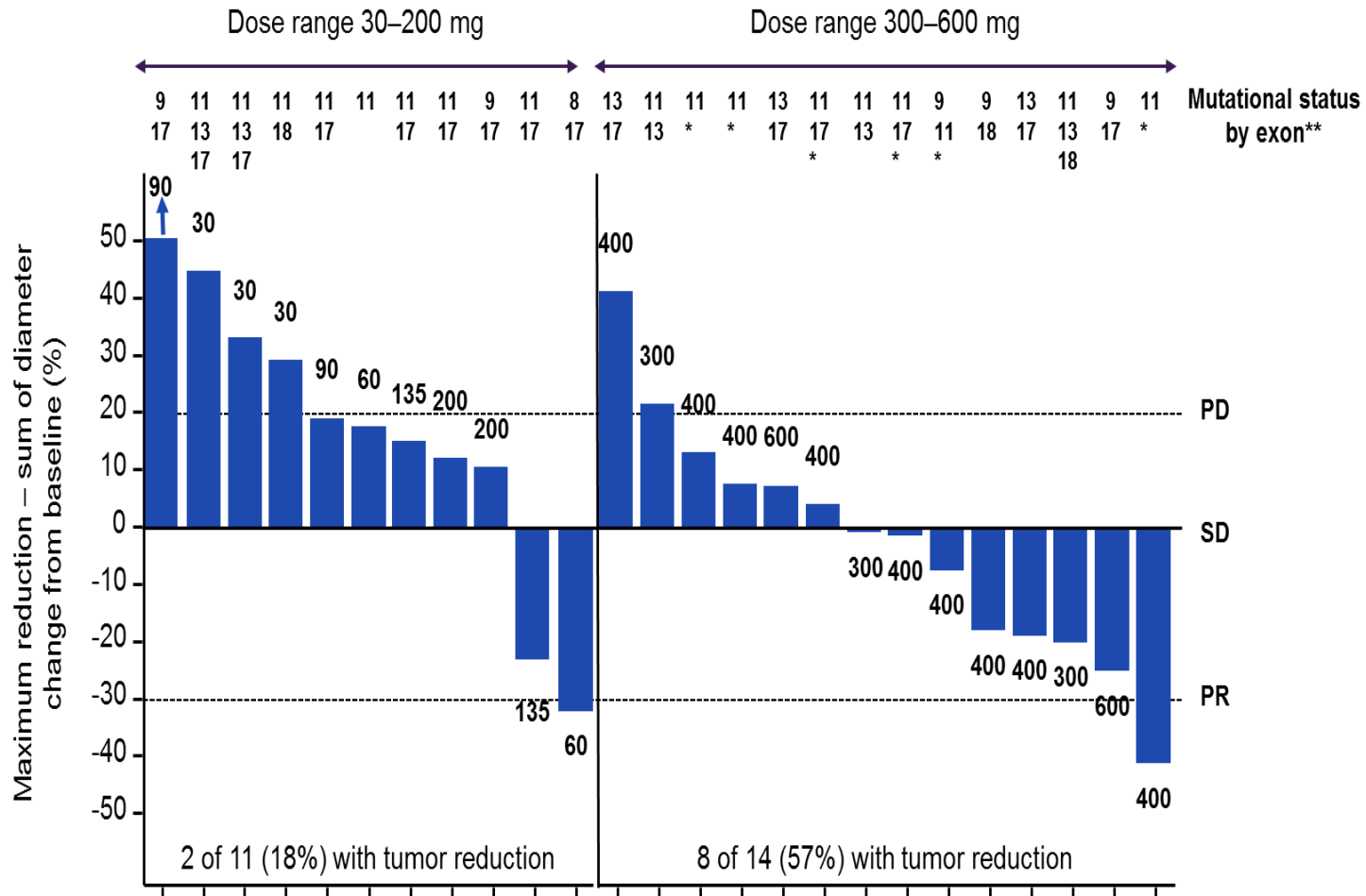
- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI PR (density -53%); RECIST SD (-21%)

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

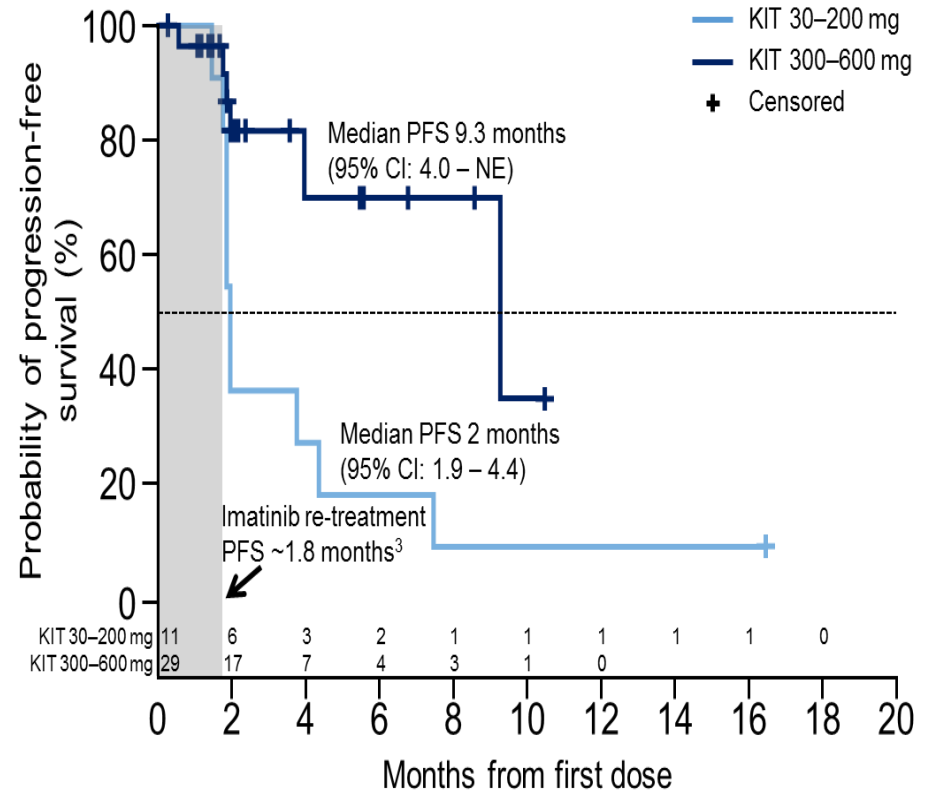
## Central radiographic review

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 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 from BLU-285 ASCO Presentation

- BLU-285 is well tolerated on a QD schedule at doses up to the MTD of 400 mg
- BLU-285 has strong clinical activity in PDGFR $\alpha$  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 (BLU-285 vs. regorafenib)

2017 ASCO - Abstract 2515, Board #7

# Pharmacokinetic-driven phase I study of DCC-2618 a pan-KIT and PDGFR inhibitor in patients (pts) with gastrointestinal stromal tumor (GIST) and other solid tumors

Filip Janku, Albiruni Abdul Razak, Michael S. Gordon, David Brooks, Daniel Flynn, Michael Kaufman, Jama Pitman, Bryan Smith, Neeta Somaiah, John De Groot, Guo Chen, Julia Jennings, Samer Salah, Deb Westwood, Eric Gerstenberger, Oliver Rosen, Suzanne George

THE UNIVERSITY OF TEXAS  
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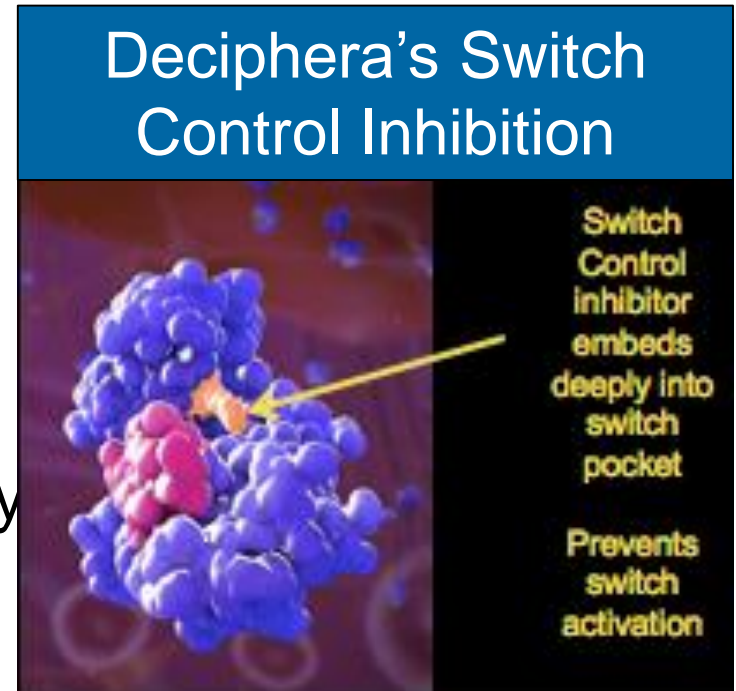
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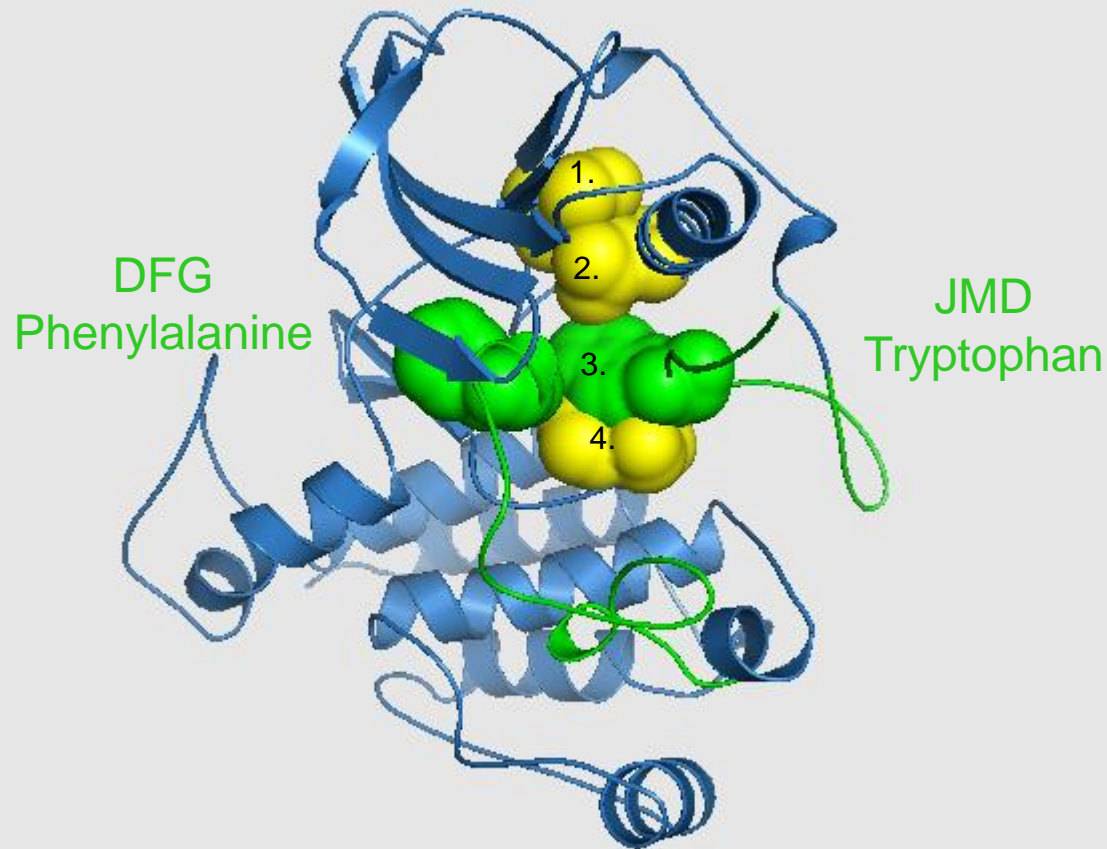
# DCC-2618 BACKGROUND

- DCC-2618 is a *KIT* and *PDGFRA* inhibitor resilient to gain-of-function and drug resistance mutations
  - Potency independent of ATP concentration
- DCC-2618 was designed to potently inhibit a broad range of mutations in *KIT* and *PDGFRA* kinases
- Gastrointestinal stromal tumor (GIST) is an important disease to achieve proof-of-concept in the FIH study due to the multiplicity and heterogeneity of resistance mutations within *KIT*





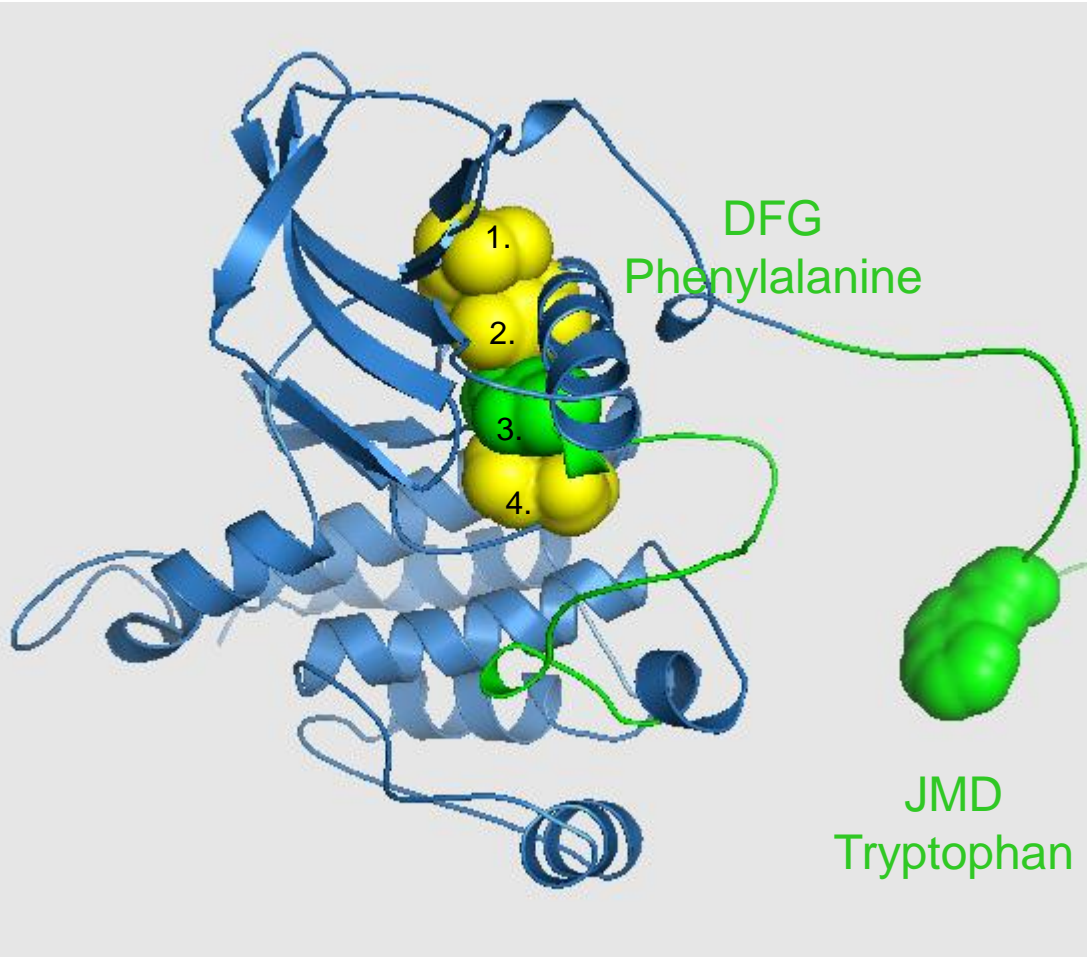
# JM-Inhibited Inactive Kinase



Snapshot 1. The rightmost green residue from the inhibitory JMD switch occupies the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this conformation, KIT kinase is in its OFF state. Note that the 'DFG' phenylalanine amino acid (green) is in the left-most position, blocking the ATP pocket.

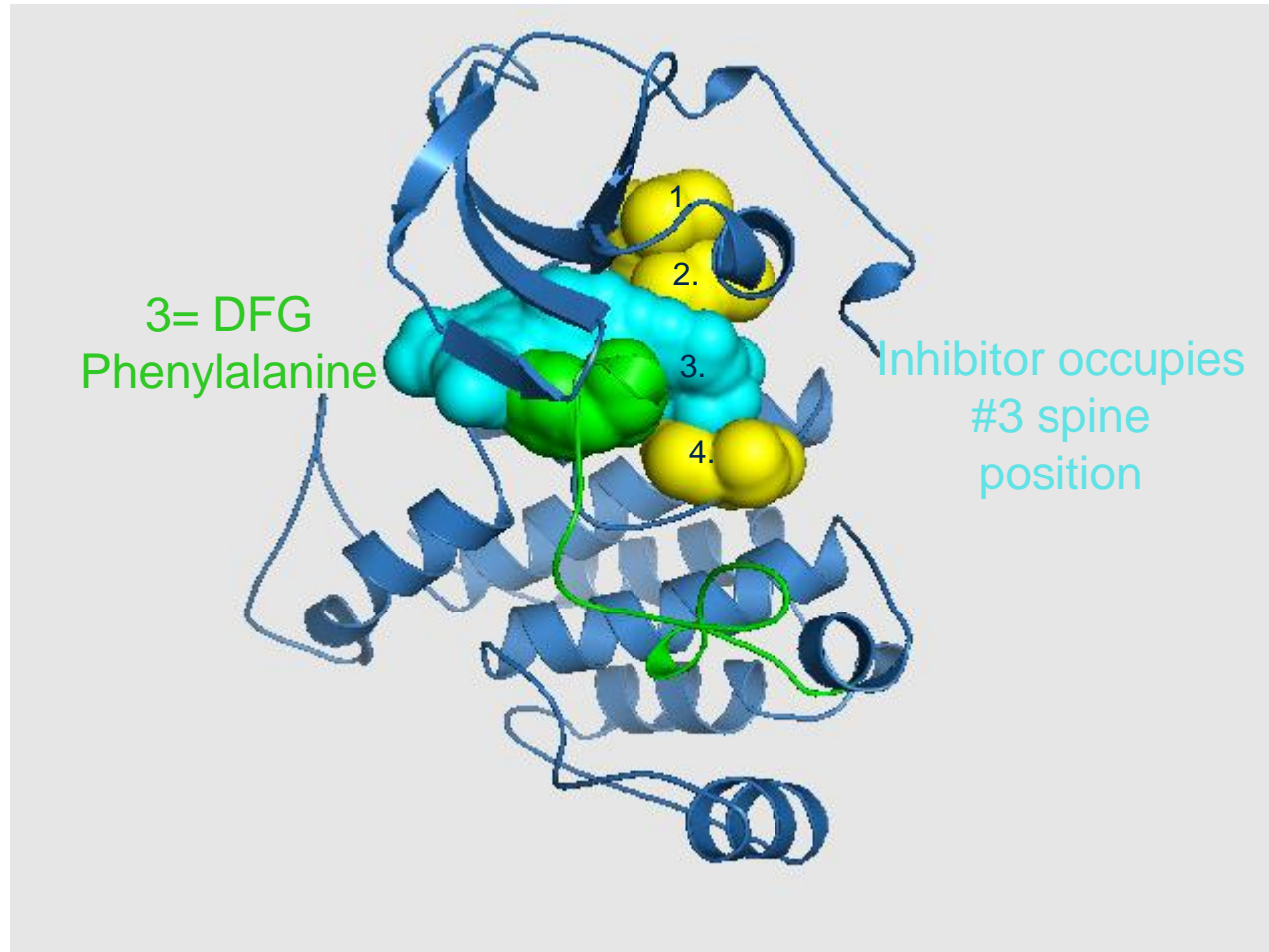
# Activated Kinase Structure



Snapshot 2. The rightmost green residue from the inhibitory JMD switch has been moved out of the #3 position in the kinase vertical spine (the other three spine residues are shown in yellow).

In this conformation, KIT kinase is in its ON state. Note that the 'DFG' phenylalanine amino acid (green) is now in the #3 position in the vertical spine.

# Switch Pocket Inhibitor Locks Kinase Into Inactive Conformation



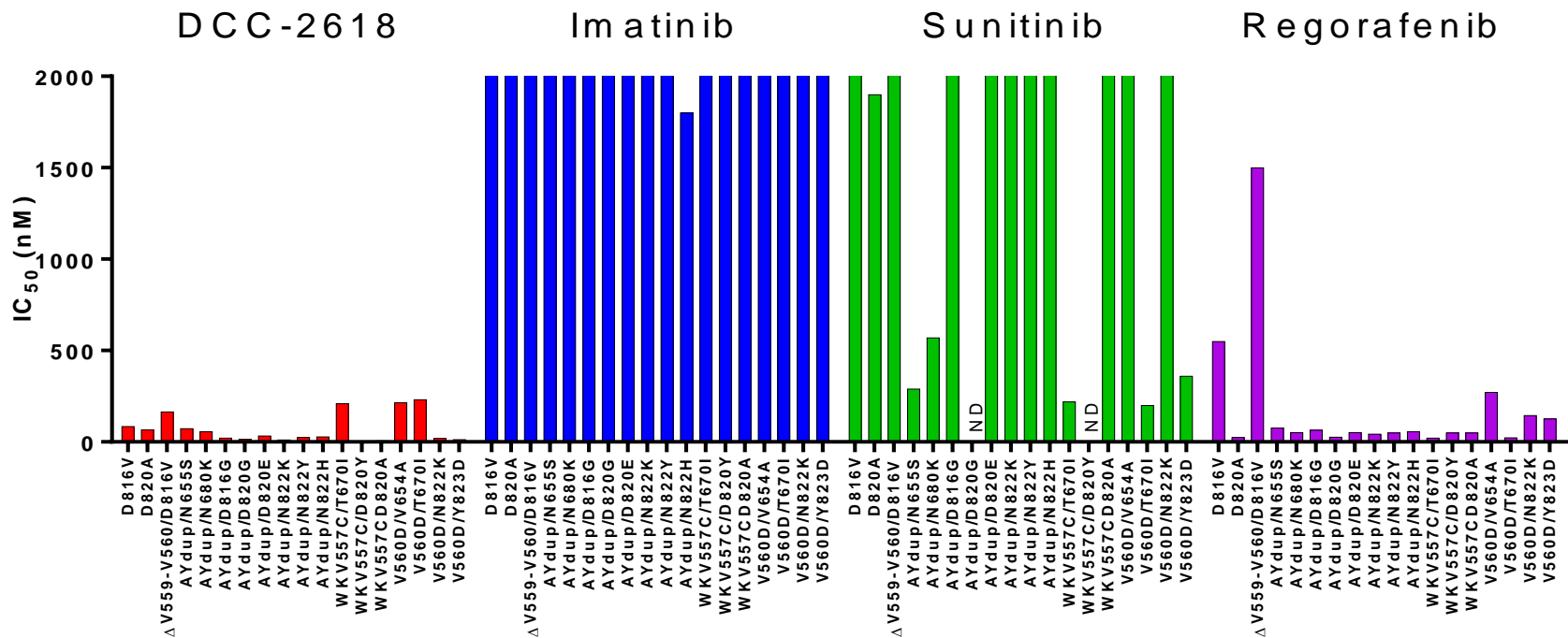
Snapshot 5. Switch Pocket Inhibitor binds to mutant KIT, with part of the inhibitor structure (blue) occupying the #3 position of the spine. This binding mode provides a biomimetic surrogate for the deleted inhibitory switch of mutant KIT.

The 'DFG' phenylalanine residue (green) is forced to occupy the out/inhibited conformation.

# RATIONALE FOR DCC-2618 STUDY

- Activity regardless whether primary mutation is in *KIT* Exon 9, Exon 11, or Exon 17
  - $IC_{50}$  for *KIT* Exon 11 deletion 3 nM,  $IC_{50}$  *PDGFRA* D842V 60 nM
- Broad activity in secondary *KIT* mutations across Exons 13, 14, 17, and 18
  - Active metabolite DP-5439 possesses comparable activity across all mutations
- KIT* T670I and V654A secondary mutations are the least sensitive to DCC-2618

## CHO *KIT* Mutant Assays



# DCC-2618-01-001: DESIGN AND OBJECTIVES

- **Design (NCT02571036)**
  - Pharmacologically-guided 3+3 escalation phase I study of oral DCC-2618 administered BID every 28 days
- **Objectives**
  - **Primary:** Safety, tolerability, maximum tolerated dose (MTD), dose-limiting toxicities (DLT)
  - **Secondary:** Pharmacokinetic profile, antitumor efficacy
  - **Exploratory:** Determination of *KIT* and/or *PDGFRA* mutations in plasma cell-free DNA (NGS) and serum tryptase
- **Major eligibility criteria**
  - Patients with advanced refractory cancers and molecular rationale for activity
  - ECOG 0-1
  - Adequate organ function
  - Prior KIT/PDGFR inhibitors were allowed

# DCC-2618 Dose Levels & Patient Characteristics (N=48)

Dose (mg)	Range of Cycles	# of Pts	Tumor Types and Tissue and/or Plasma cfDNA Mutations
20 BID	0-19 cycles	4	<b>GIST:</b> <i>KIT</i> Exon 11 (1x), <i>KIT</i> Exon 17 (1x), <i>PDGFRα</i> (1x) <b>GBM:</b> <i>PDGFRα</i> / <i>KIT</i> / <i>KDR</i> co-amplified (1x)
30 BID	0-13 cycles*	4	<b>GIST:</b> <i>KIT</i> Exon 11 (1x), <i>KIT</i> Exon 11 & 17 (1x) <b>Thymic Carcinoma:</b> <i>KIT</i> Exon 11 (1x) <b>Desmoid tumor</b> (1x)
50 BID	0-13 cycles	6	<b>GIST:</b> <i>KIT</i> Exon 9 (1x), <i>KIT</i> Exon 11 (3x) <b>Astrocytoma:</b> <i>PDGFRα</i> / <i>KIT</i> / <i>KDR</i> co-amplified (1x) <b>GBM:</b> <i>PDGFRα</i> / <i>KIT</i> / <i>VEGFR2</i> co-amplified (1x)
100 BID	0-12 cycles*	7	<b>GIST:</b> <i>KIT</i> Exon 9 (3x), <i>KIT</i> Exon 11 (1x), <i>PDGFRα</i> (1x), <i>SDHA</i> (1x) <b>Gyn SSC:</b> <i>PDGFRα</i> / <i>KIT</i> / <i>KDR</i> co-amplified (1x)
150 BID	0-8 cycles	6	<b>GIST:</b> <i>KIT</i> Exon 9 (2x), <i>KIT</i> Exon 11 (3x), <i>KIT</i> Exon 17 (1x)
200 BID	0-3 cycles	7	<b>GIST:</b> <i>KIT</i> Exon 9 (4x), <i>KIT</i> Exon 11 (3x)
100 QD	0-7 cycles	6	<b>GIST:</b> <i>KIT</i> Exon 11 (1x), <i>KIT</i> Exon 11 & 13 (1x) <b>Adenoid Cystic Carcinoma:</b> <i>PDGFRα</i> / <i>KIT</i> / <i>VEGFR2</i> amplified (1x) <b>GBM:</b> <i>PDGFRα</i> (2x) <b>SM:</b> <i>KIT</i> Exon 17 (1x)
150 QD	0-6 cycles	8	<b>GIST:</b> <i>KIT</i> Exon 9 (1x), <i>KIT</i> Exon 11 (2x), <i>KIT</i> Ex 9 & 17 (1x), <i>KIT</i> Exon 11 & 13 (1x), <i>KIT</i> Exon 11 & 17(1x), <i>PDGFRα</i> (2x)
		<b>48</b>	mean of <b>4.7</b> prior therapies

\*Patient stayed on study following PD due to clinical benefit

Cutoff date – 08/May/2017

# Summary of TEAEs by Grade [ $\geq 5$ ( $\geq 10\%$ )]\*

## Grade 3/4 by Cohort - All Grades Regardless of Causality

Event Term	Total Events	Grade 1/2
Fatigue	22	21
Alopecia	13	13
<b>Anaemia</b>	13	6
<b>Lipase increased</b>	12	6
Decreased appetite	11	10
Abdominal pain	9	8
Dyspnoea	9	9
Weight decreased	9	9
Amylase increased	8	7
Nausea	8	8
Arthralgia	7	7
Constipation	7	7
Diarrhoea	7	7
<b>Hypertension</b>	7	4
<b>Myalgia</b>	7	7
Vomiting	7	6
Blood bilirubin increased	6	5
Cough	6	6
<b>Blood creatine phosphokinase increased</b>	5	3
Hypokalaemia	5	4
Urinary tract infection	5	4

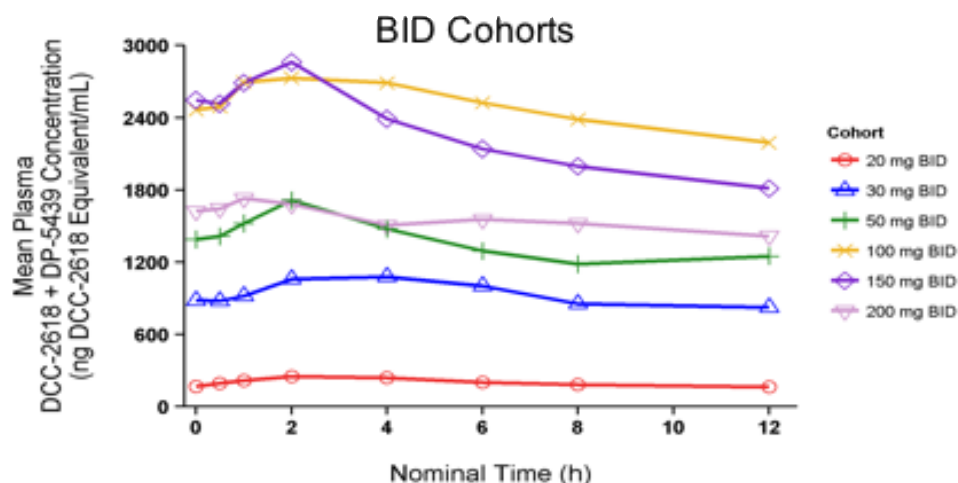
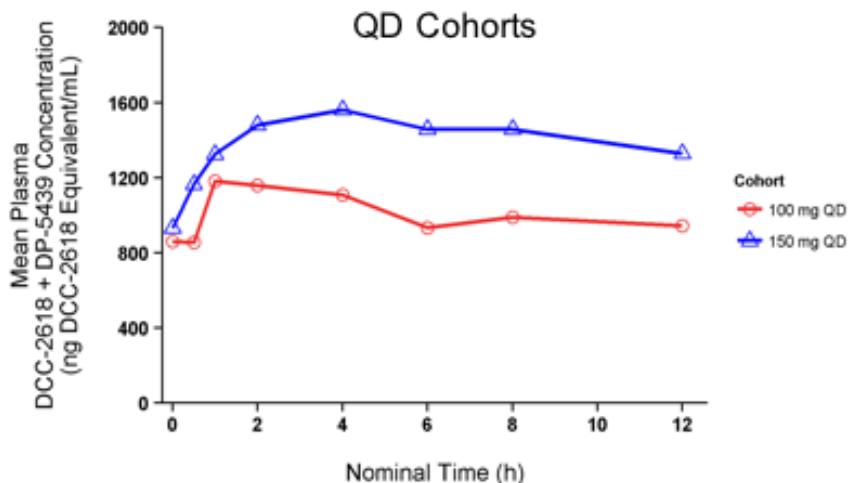
Grade 3 & 4	20mg BID (N=4)	30mg BID (N=4)	50mg BID (N=6)	100mg BID (N=7)	150mg BID (N=6)	200mg BID (N=7)	100mg QD (N=6)	150mg QD (N=8)
1			1					
7		1	2	2	2			
6	1			2		1	1	1
1							1	
1							1	
1							1	
3				1	1	1		
1					1			
1								1
2		1						1
1			1					
1					1			

- All lipase and creatine phosphokinase elevations were not clinically significant.
- Two G3 lipase elevations and a G4 creatine phosphokinase elevation were DLTs and occurred at 100 mg & 200 mg BID and 150 mg QD, respectively.

\* Data Cut 08/May/2017



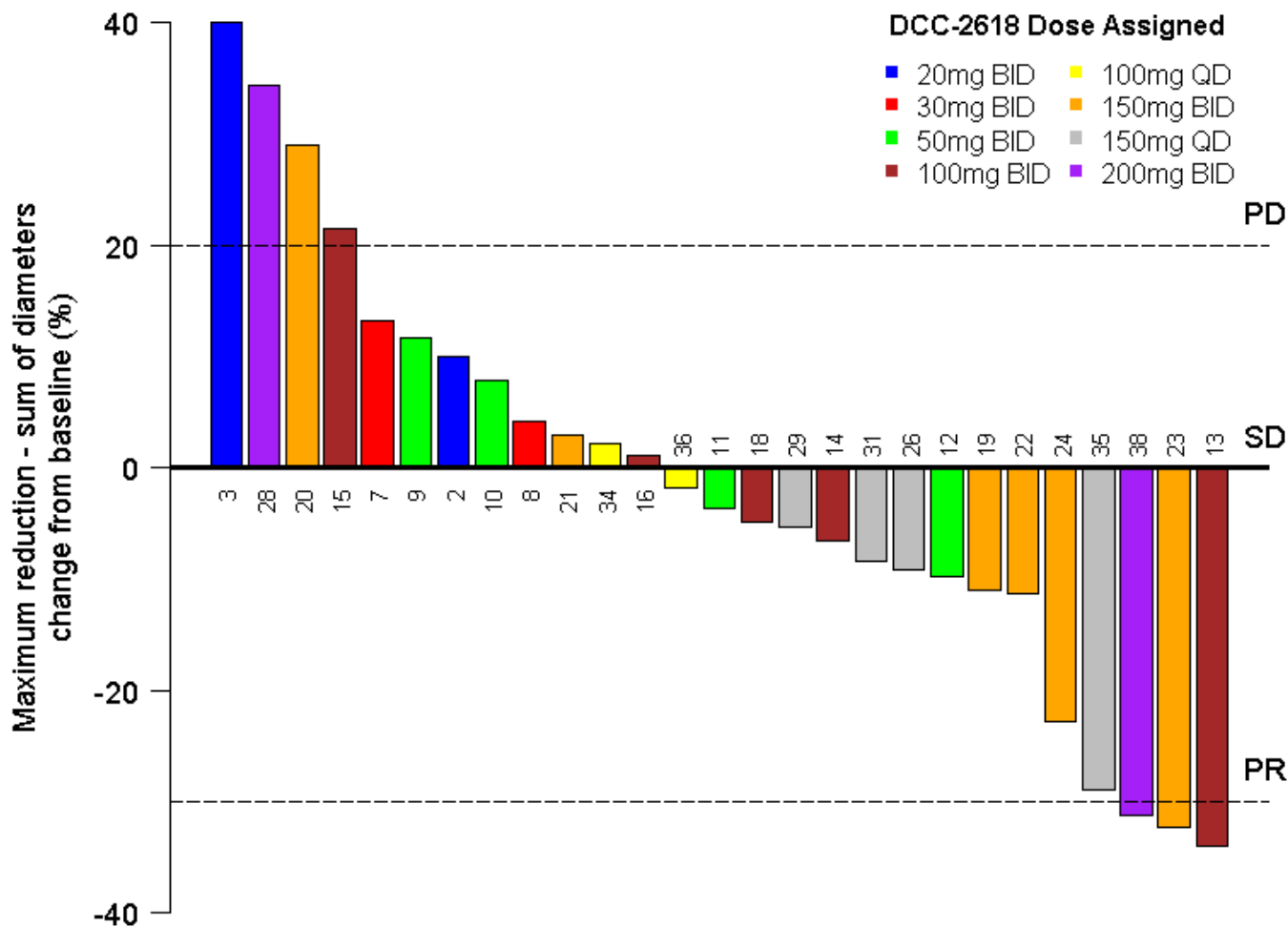
# Cycle 1 Plasma Pharmacokinetics Total Exposure Across QD and BID Dosing Cohorts (N=48)



- DP-5439, an active metabolite of DCC-2618, exhibits comparable activity across all KIT mutations and substantially contributes to total drug exposure.
- QD dose cohorts show a dose proportional increase in total exposure from 100 to 150 mg.
- BID dose cohort exposures are dose proportional from 30 to 100 mg BID and then plateau from 100 to 200 mg BID.
- At doses as low as 50 mg BID, reductions in cfDNA were observed across KIT mutations (Fig 6) that include those mutations with the highest in vitro  $IC_{90}$  values to DCC-2618 (data not shown)
- Comparison of Day -7 (Fed) to Cycle 1 Day 1 (Fasted) support administration of DCC-2618 with or without food (data not shown).



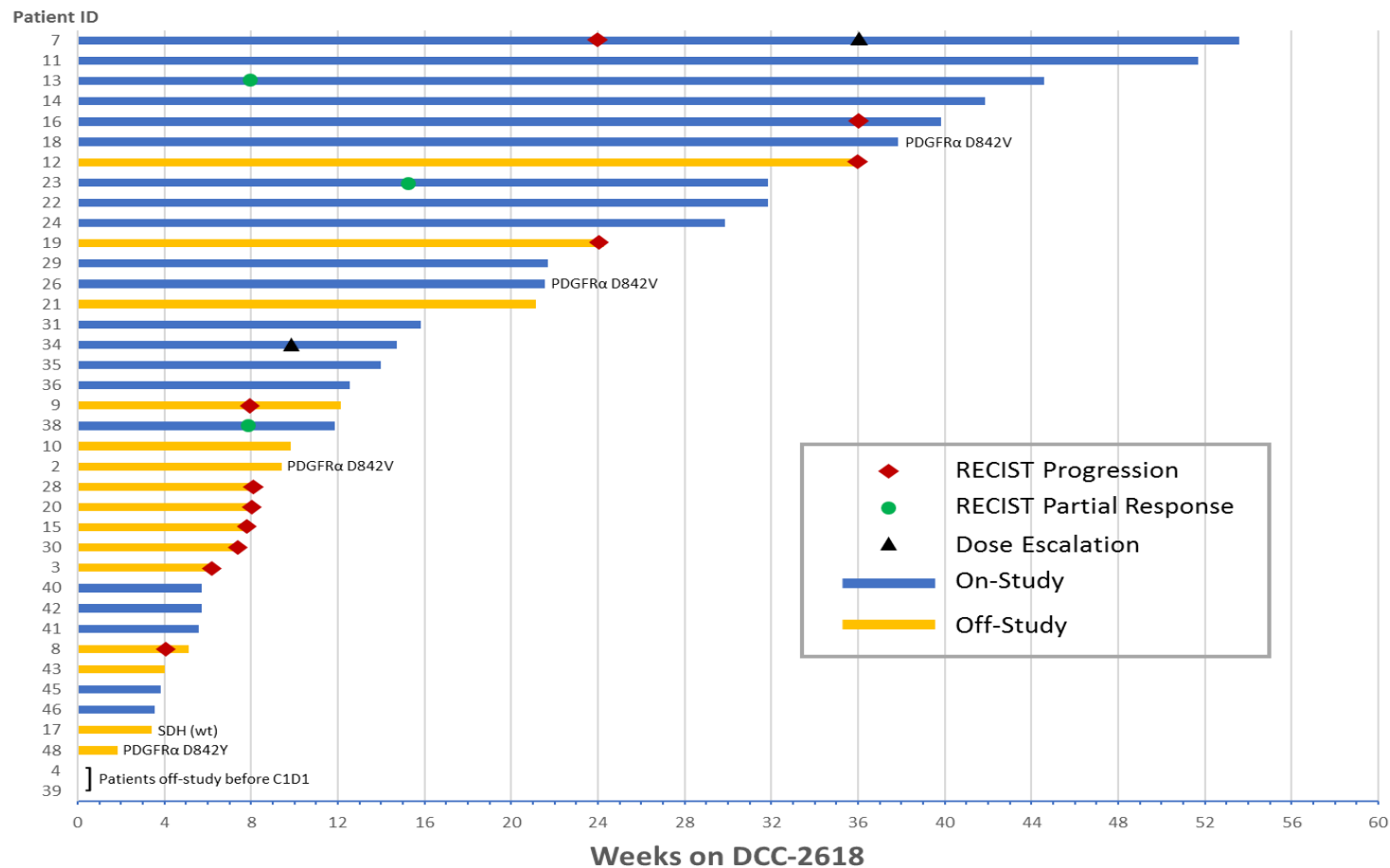
# Waterfall Plot (Best Response, N=27)



Notes: GIST patients only. Data as recorded in EDC. Patient 3 had a 66% increase in tumor size.  
 PD = Progressive disease. SD = Stable disease. PR = Partial response.

Cut off May 8<sup>th</sup>, 2017

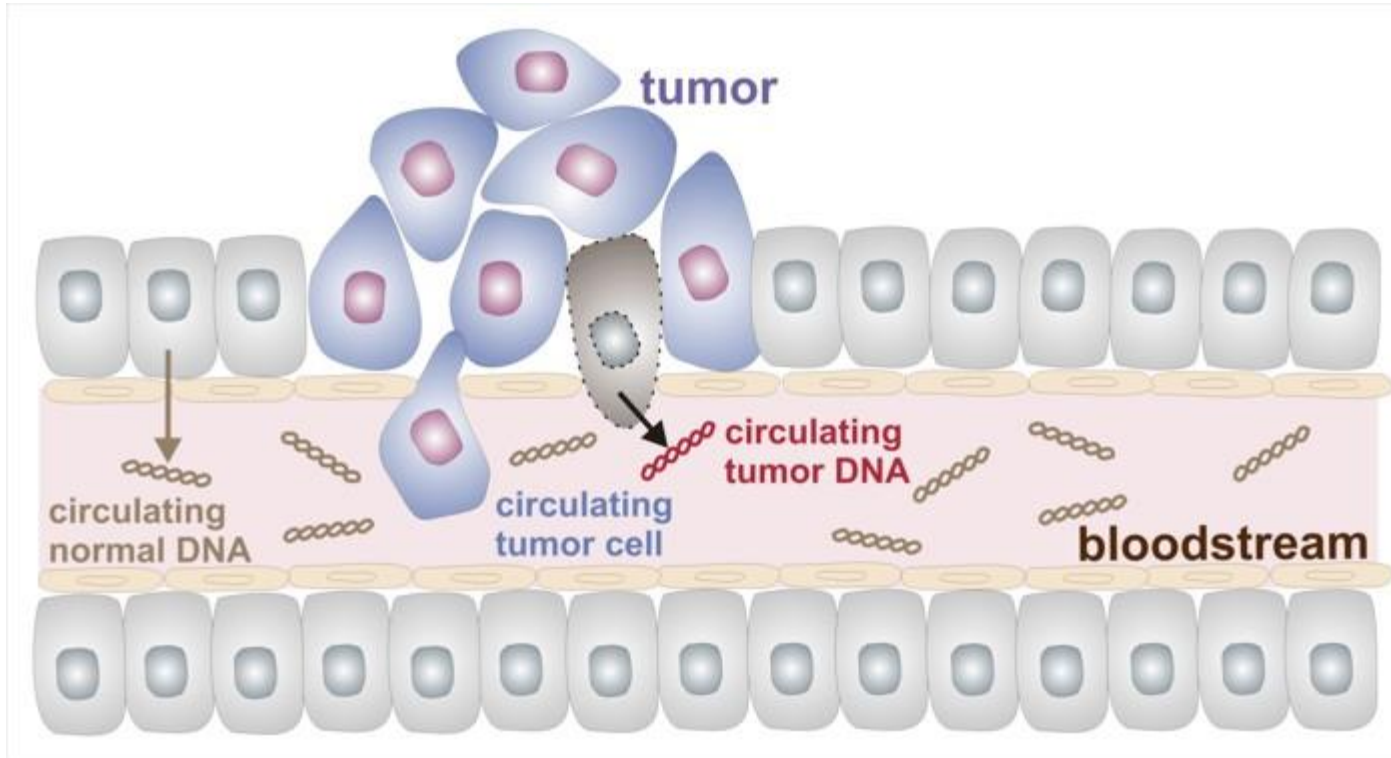
# Duration of Treatment on DCC-2618 – All GIST Patients (N=38)



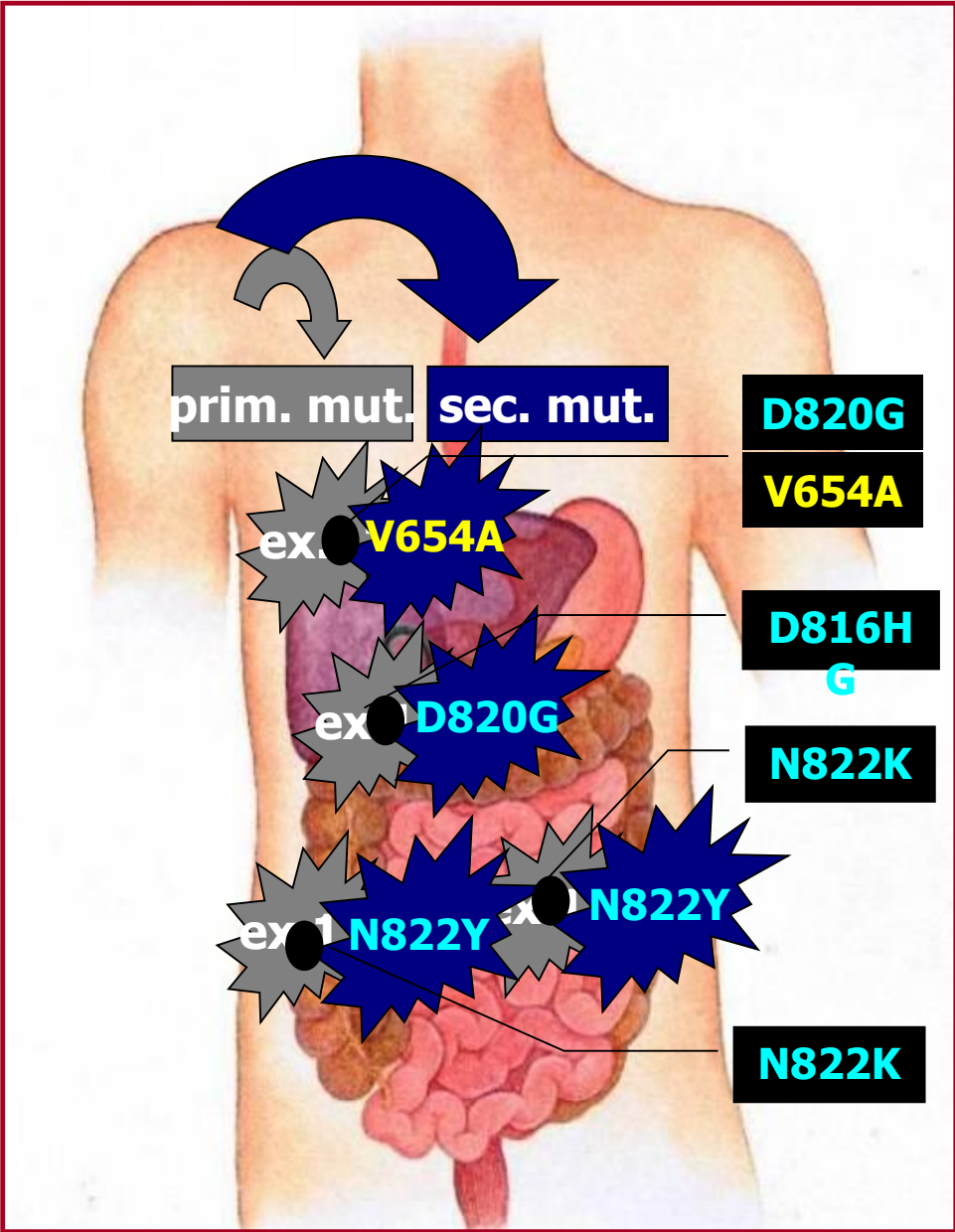
The Disease Control Rate (DCR) for KIT- and PDGFRα GIST cohorts for daily dose equivalents of ≥100 mg

- at 6 months is 60% (9/15 patients)
- at 3 months is 78% (18/23 patients)

# Circulating Tumor DNA (ctDNA)



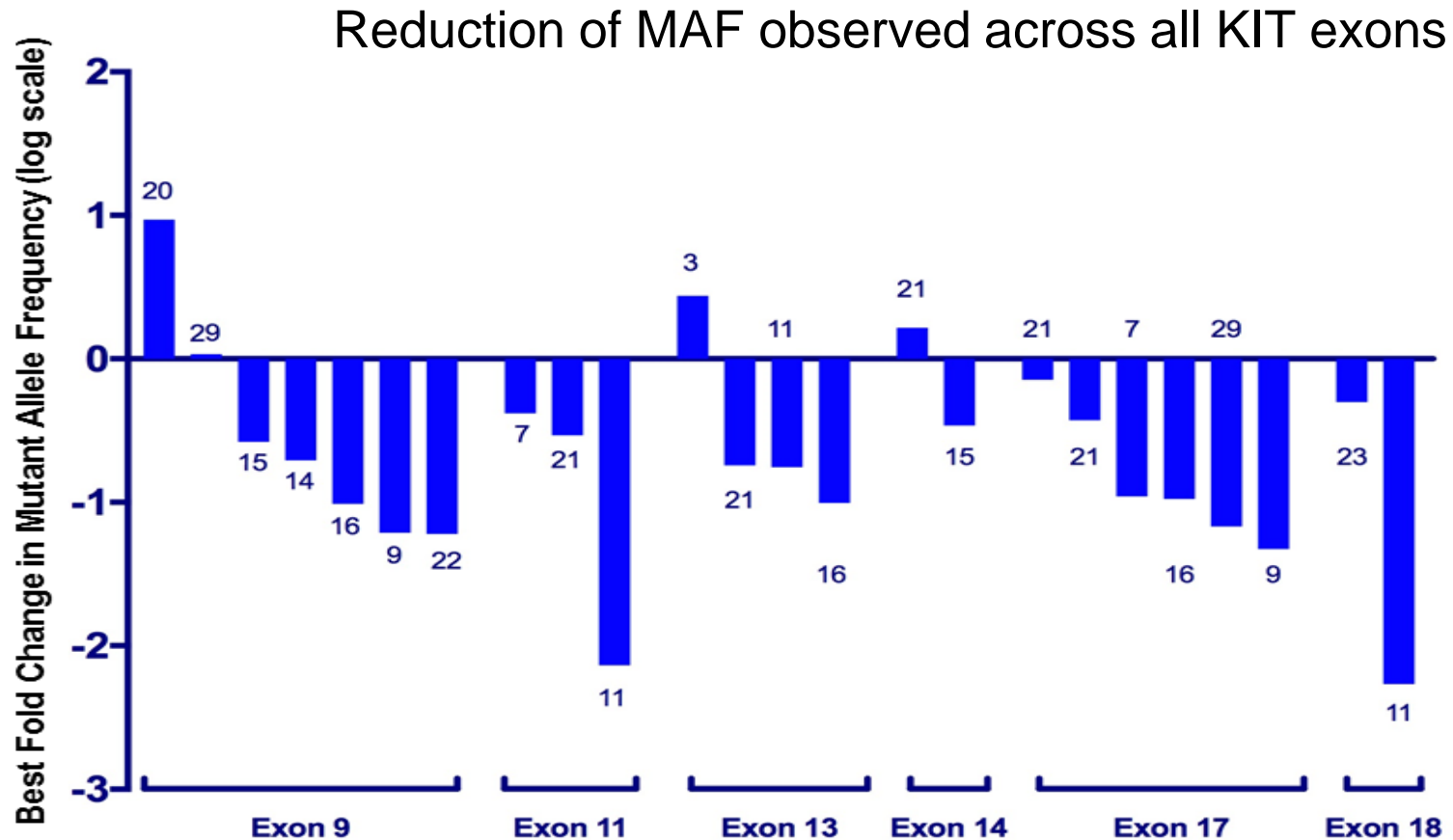
# Implications of Mutational Heterogeneity



**Drug/ATP binding pocket**  
Imatinib resistant  
Sunitinib sensitive

**Kinase activation loop**  
Imatinib resistant  
Sunitinib resistant

# Use of cfDNA as Pharmacodynamic Biomarker to Demonstrate pan-KIT Activity of DCC-2618 in KIT GIST Patients (N=12)



- Waterfall plot of best response for MAF reductions for Exons 9, 11, 13, 14, 17, and 18 (reduction from baseline; log scale for Y axis); only patients with detectable plasma cfDNA and follow up are included.
- Several patients harbored multiple mutations (see patient numbers at each bar).

# Conclusions from DCC-2168 ASCO Presentation

- DCC-2618 is well tolerated up to 200 mg BID.
  - No patient discontinued DCC-2618 due to toxicity.
  - All DLTs were clinically insignificant.
- DCC-2618 produced encouraging disease control with objective responses and prolonged stable disease in heavily pre-treated GIST patients.
  - The DCR for KIT- and PDGFR $\alpha$  GIST for cohorts for daily dose equivalents of  $\geq 100$  mg at 6 months is 60% (9/15 patients), and at 3 months is 78% (18/23 patients).
- Notable reductions in MAF of imatinib resistance mutations across all relevant exons in KIT suggests activity across a wide range of imatinib resistance mutations in advanced GIST.
- 150 mg QD is the recommended dose of DCC-2618 for the Phase 1 expansion stage, which includes the following cohorts:
  - Patients with GIST who have progressed on or are intolerant of imatinib.
  - Patients with advanced systemic mastocytosis.
  - Patients with other KIT- and PDGFR $\alpha$  driven diseases e.g., gliomas.
- Based on these data, a randomized phase 3 study is planned for treatment of patients after imatinib, sunitinib, and regorafenib

# Summary

- BLU-285 and DCC-2618 are novel potent KIT inhibitors with unprecedented activity against KIT exon 17 mutations
  - Both drugs have pre-clinical activity against primary KIT mutations as well as KIT exon 13 and 14 mutations
- Both drugs appear safe and tolerable and have moved from dose-escalation to dose-expansion phases of clinical study
- In the future, circulating tumor DNA tests may be useful clinically to follow the status of GIST patients being treated with kinase inhibitors
  - Although some of these tests are clinically available, it is premature to use them to guide drug therapy
- Currently, both studies are open at OHSU (and other sites)
  - Contact my study nurse (Tracy Walker) at [walkertr@ohsu.edu](mailto:walkertr@ohsu.edu) or 503-346-1183 if you are interested in being considered for these studies
- Both drugs will be further studied in phase 3 studies that will open in late 2017 or early 2018

# Acknowledgement

- Blueprint Medicines for sharing slides and data
- Deciphera Pharmaceuticals for sharing slides and data
- Patients, families, investigators, and study team support members who participated in the ongoing BLU-285 and DCC-2618 studies