Emerging Therapies and Ongoing Trials in Metastatic GIST Part II

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  - Blueprint Medicines, Deciphera

- Scientific Advisory Board Member/Consultant:
  - Blueprint Medicines, Deciphera

Current approved therapies for advanced GIST

- Imatinib – relatively narrow spectrum TKI, excellent inhibition of KIT exon 11, less potent exon 9 - most often resistance develops due to secondary resistance KIT mutations

- Sunitinib – broader spectrum TKI, KIT exon 11, exon 9, exon 13, 14 – also VEGFR and other – challenges: secondary resistance KIT mutations, toxicity

- Regorafenib – broad spectrum, potent TKI – KIT exon 11, exon 17, VEGFR and others – challenges: secondary resistance KIT mutations, toxicities

- Duration of disease control has remained a challenge
- Likely due to heterogeneity of resistance mutations in KIT
- May also be related to adequate drug exposure
- Challenges of non-KIT directed toxicities of multi-targeted TKIs

    - Hypertension
    - Hand-Foot Skin Reaction
    - Diarrhea

Ongoing trials of two new KIT inhibitors

- BLU-285
- DCC2618

GIST: imatinib and beyond

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

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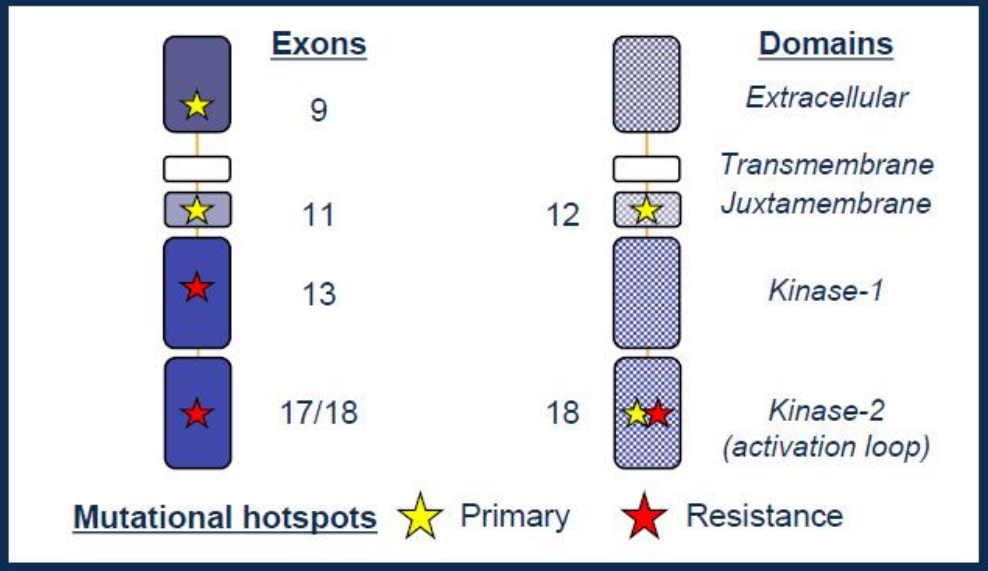
Imatinib revolutionized Gastrointestinal Stromal Tumor (GIST) treatment

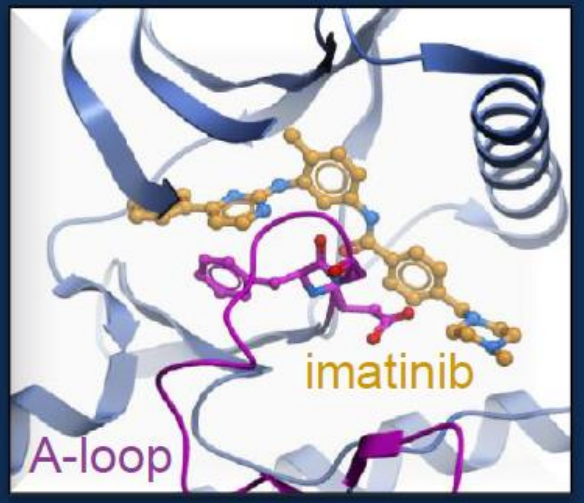
KIT PDGFRα



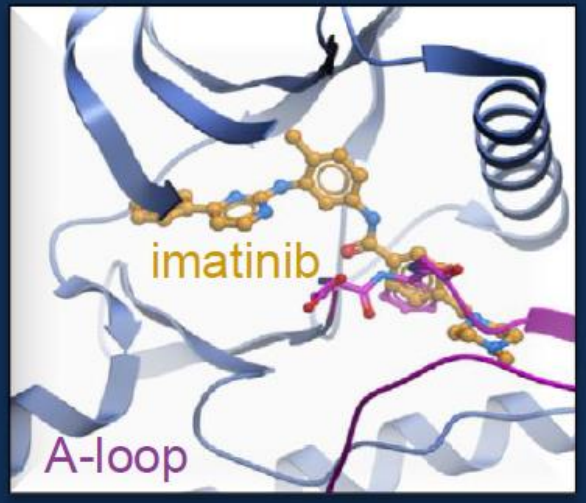
- KIT mutations drive ~75–80% of GIST
- PDGFRα mutations drive ~5–10% of GIST

KIT

Inactive conformation



Active conformation

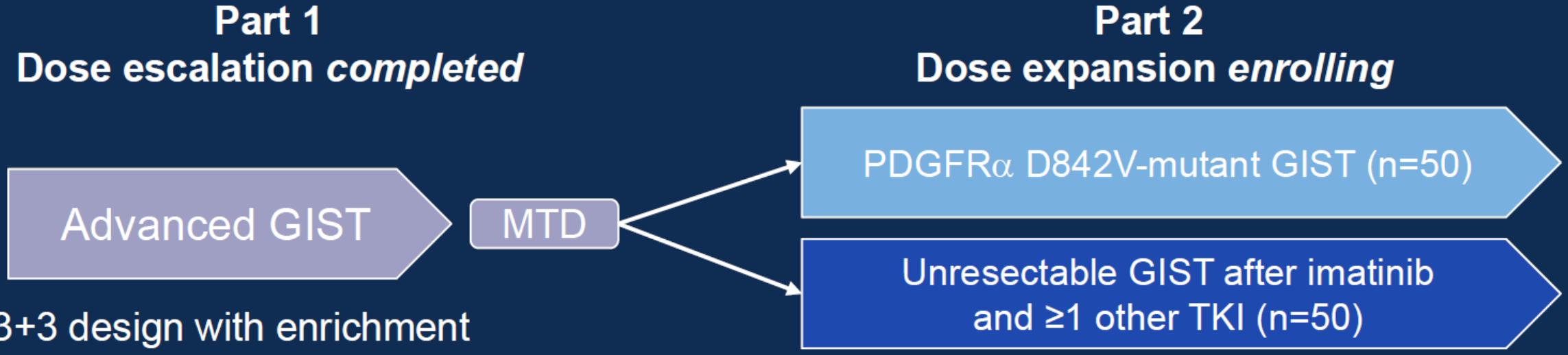


- Imatinib binds the inactive kinase conformation and inhibits many primary mutants
- Imatinib is a highly effective first-line GIST therapy

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

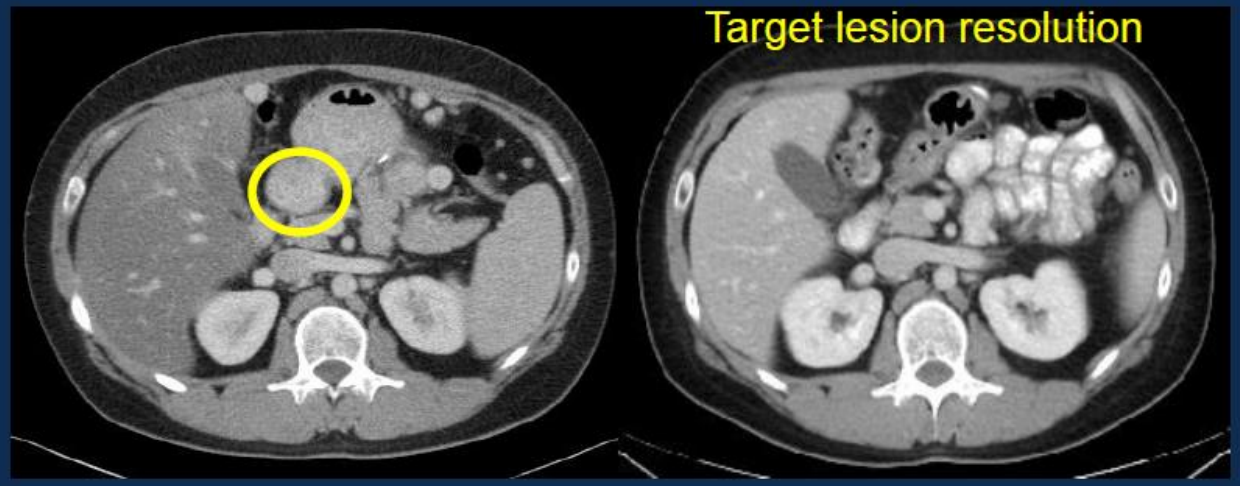
Demography and baseline patient characteristics

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

Radiographic response per RECIST 1.1 in PDGFRα D842V-mutant GIST

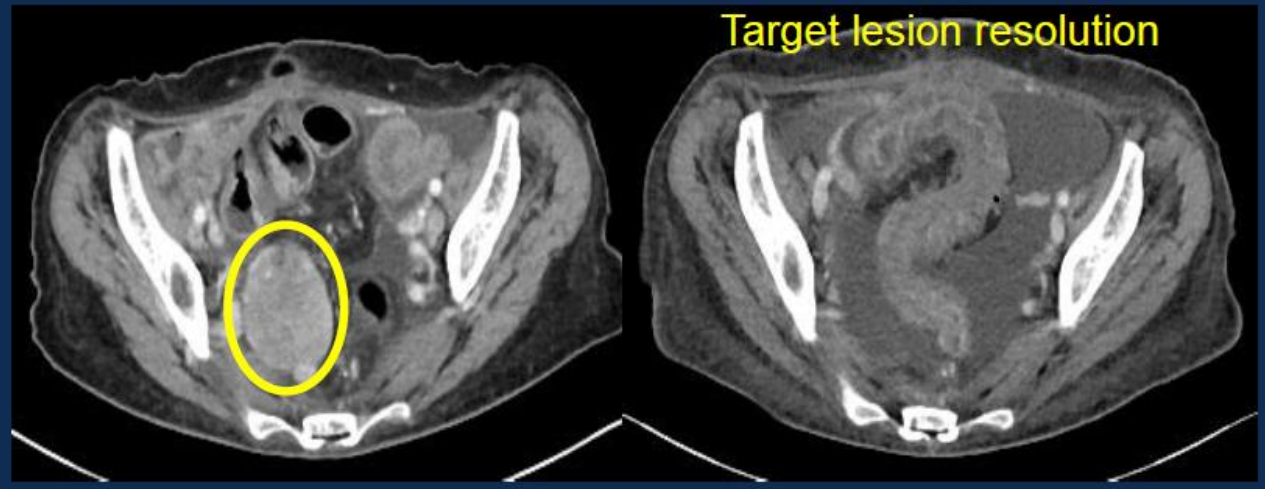
BLU-285 300 mg (dose escalation)



Baseline | After 4 months

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

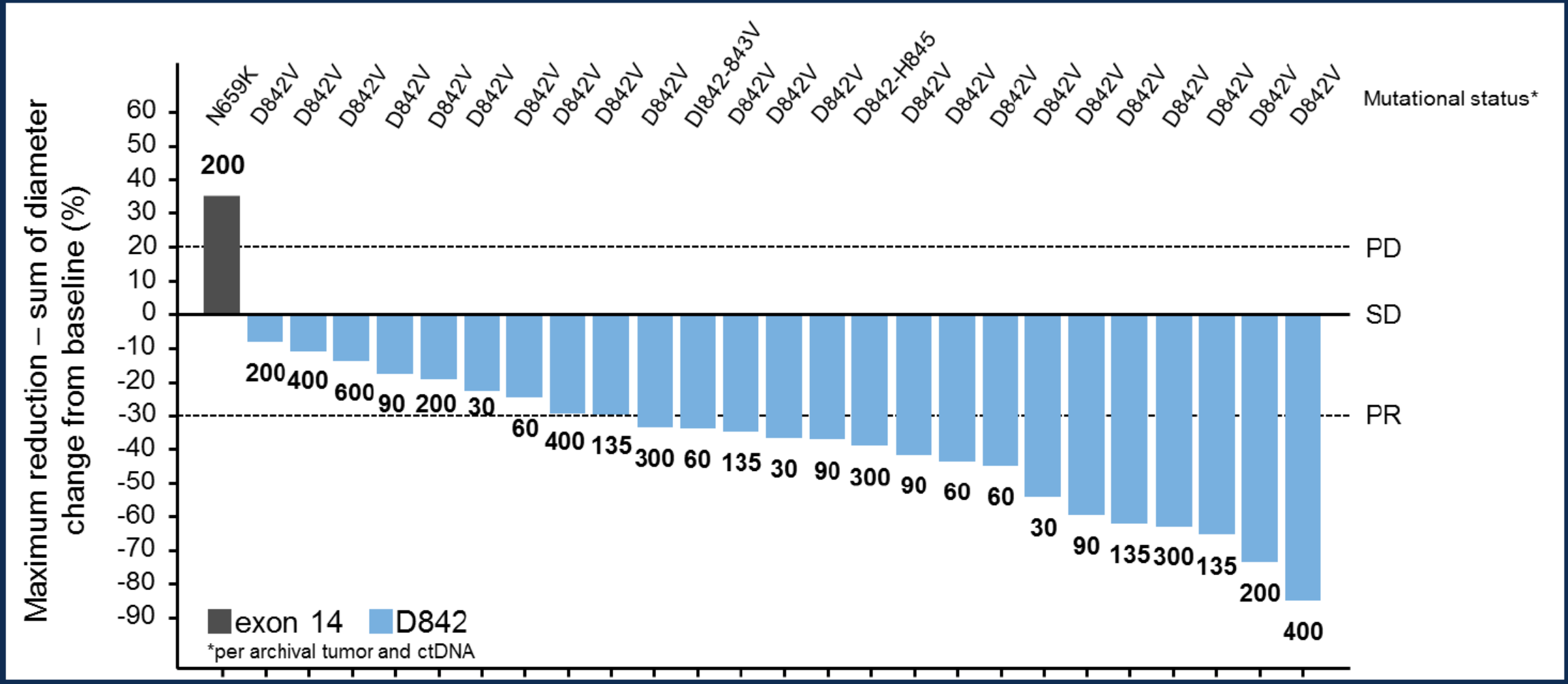
BLU-285 400 mg (dose expansion)



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)



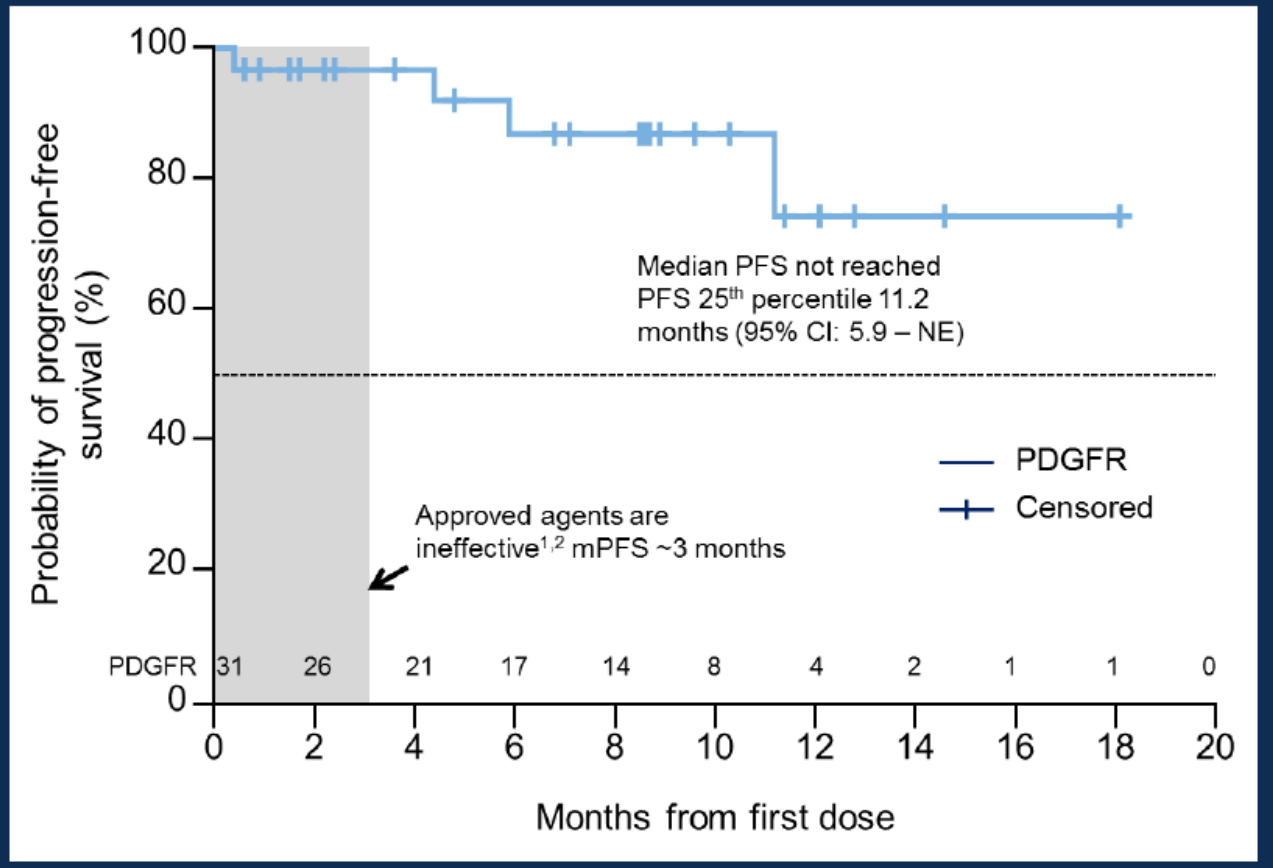
High response rate and prolonged PFS in PDGFRα D842-mutant GIST

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

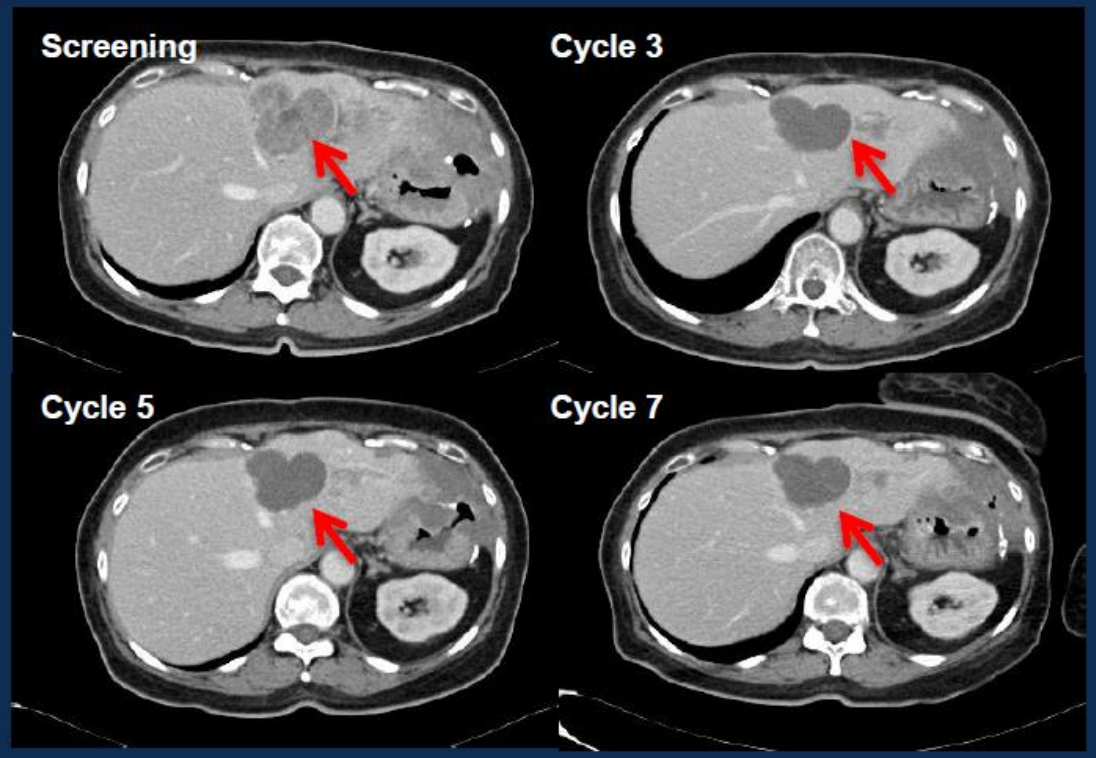
* 12 confirmed, 3 pending confirmation

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



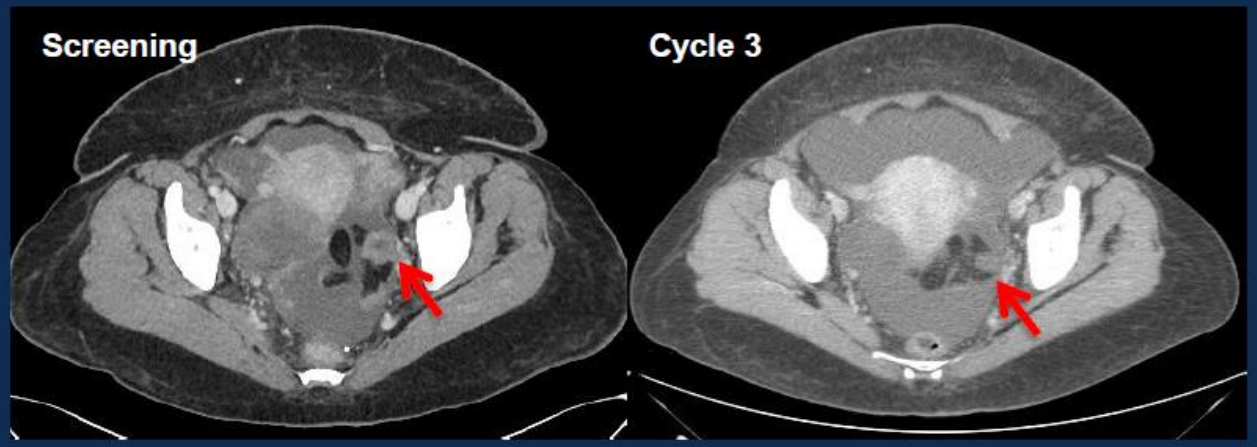
Radiographic response in heavily pre-treated KIT-mutant GIST

BLU-285 300 mg (dose escalation)



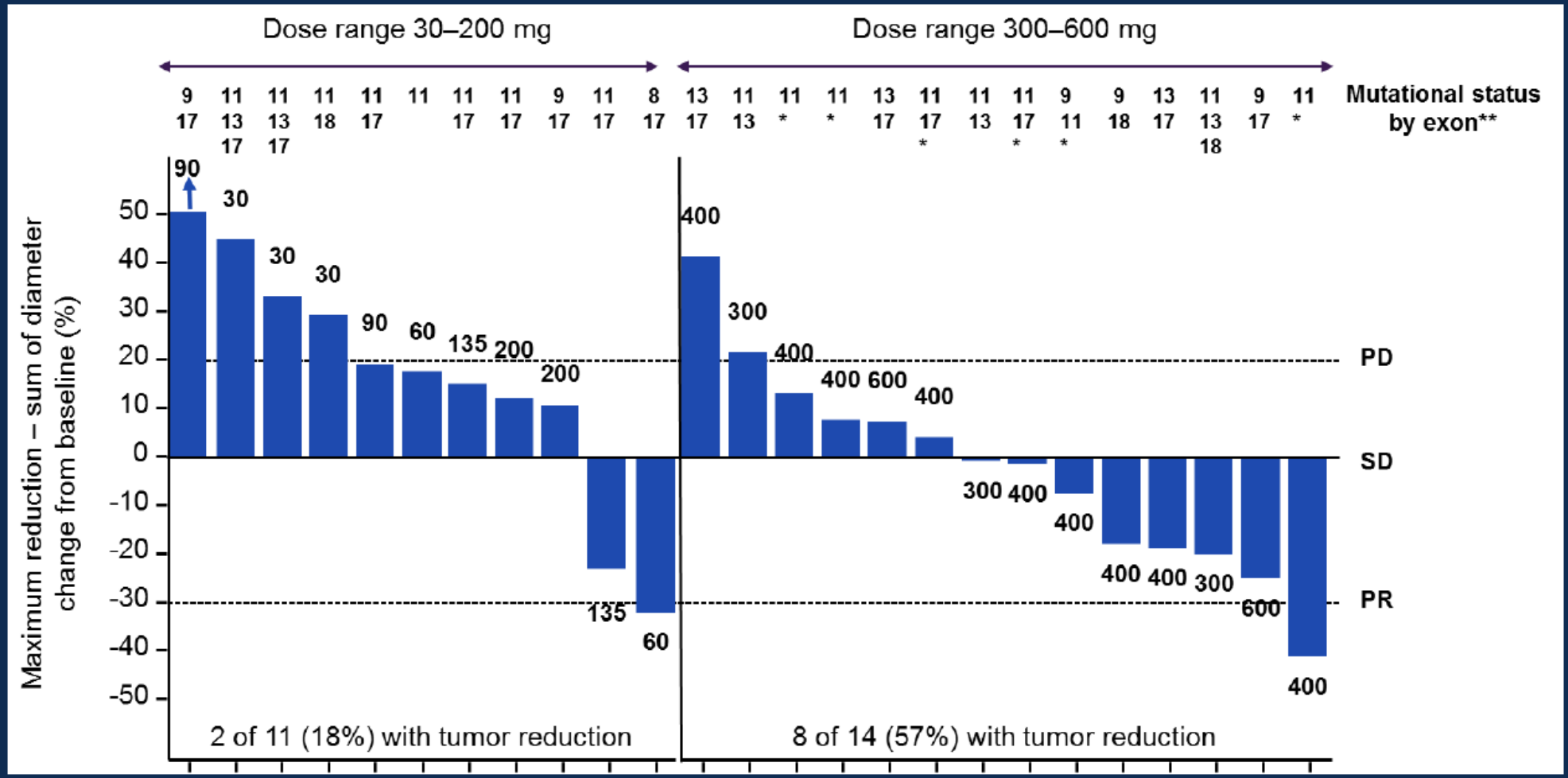
- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI PR (density -53%); RECIST SD (-21%)

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

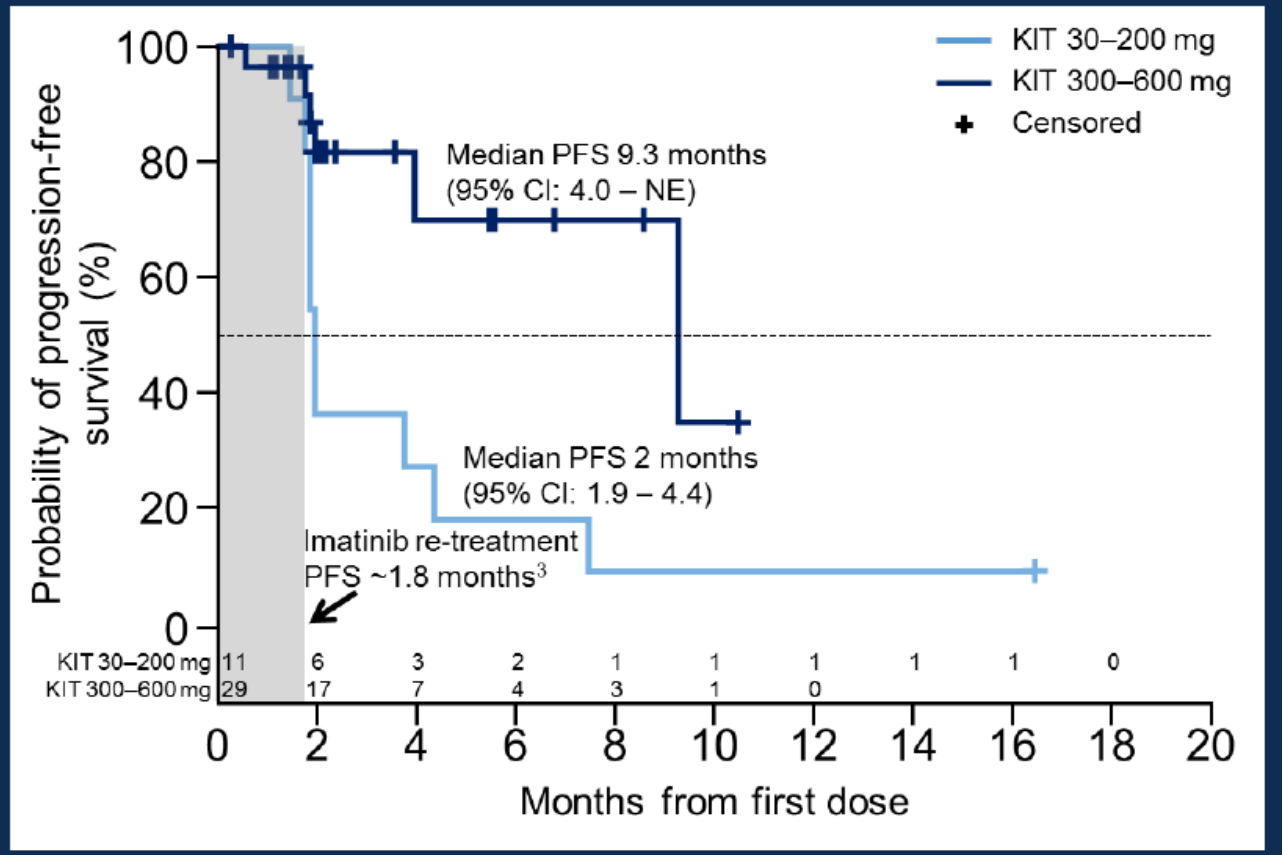
Central radiographic review

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

2017 ESMO – Proffered Paper

Encouraging activity of novel pan-KIT and PDGFRα inhibitor DCC-2618 in patients (pts) with gastrointestinal stromal tumor (GIST)

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Background and Rationale for DCC-2618 in GIST

- Approved TKIs primarily inhibit either the KIT ATP binding pocket (exon 13/14) or a subset of activation loop mutations (exon 17/18)
  - Lack of activity across both regions known to cause imatinib resistance leaves significant liabilities in inhibitory coverage
- DCC-2618 is a potent pan-KIT and PDGFRα kinase switch control inhibitor active across a broad range of mutations
- In non-clinical analyses, DCC-2618 showed activity against all initiation and resistance mutations tested
- During the escalation stage of the First-In-Human Study, 150 mg QD was selected as the recommended dose for the Phase 1 expansion stage
  - Doses of ≥100 mg/d caused reductions in mutation allele frequency in plasma cell-free DNA (cfDNA) that included the least sensitive KIT mutations
  - MTD not reached. Daily doses of up to 400 mg were tested
- The Phase 1 expansion stage is enrolling GIST Patients who have progressed on, or are intolerant to imatinib and or other TKIs

Study Design and Methods (NCT# 02571036)

- Dose-escalation study of oral DCC-2618 (QD or BID q28 days) in pre-treated TKI resistant GIST followed by expansion cohorts (cut-off July 28, 2017)
- Tumor assessment: CT scans every 2 cycles per local assessment
  - Escalation phase only: FDG-PET scans at baseline and after 3 weeks of therapy
- Next generation sequencing (NGS) of plasma cfDNA was performed throughout the study to quantify KIT, PDGFRα and other molecular alterations
- Tumor tissue was obtained at baseline for NGS analysis of mutational status

Patients (Major Eligibility Criteria)

- Patients with advanced refractory cancers with a focus on GIST patients
- ECOG 0-1; adequate end organ function
- Prior KIT/PDGFRα inhibitors were allowed

DCC-2618 Safety Population - Summary of TEAEs
(Treatment-Emergent AE / Regardless of Causality) ≥10% (N=70)

Event Term	Total Events	<100 mg/d (N = 8)		≥ 100 mg/d (N = 62)		150mg QD (N = 21)	
		G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Lipase increased	33	5	1	15	12	3	2
Fatigue	32	6	0	25	1	5	0
Anaemia	29	1	1	9	18	0	1
Decreased appetite[$]	20	1	0	17	1	3	0
Diarrhoea	16	1	0	15	0	0	0
Alopecia	15	1	0	14	0	4	0
Hypertension	15	0	1	9	5	0	0
Amylase increased	14	3	0	10	1	1	0
Myalgia	14	2	0	12	0	2	0
Weight decreased	14	1	0	13	0	1	0
Dyspnoea[#]	13	4	0	8	1	1	0
Abdominal pain	11	3	0	7	1	0	0
Constipation	11	4	0	7	0	2	0
Nausea	11	2	0	9	0	1	0
Palmar-plantar erythrodysaesthesia syndr.	11	0	0	11	0	2	0
Arthralgia	10	2	0	8	0	0	0
Blood bilirubin increased	10	1	0	7	2*	0	1*
Rash	8	2	0	6	0	1	0

All DLT events were not clinically significant: 2 G3 lipase ↑ at 100 mg & 200 mg BID and a G4 CPK ↑ at 150 mg QD

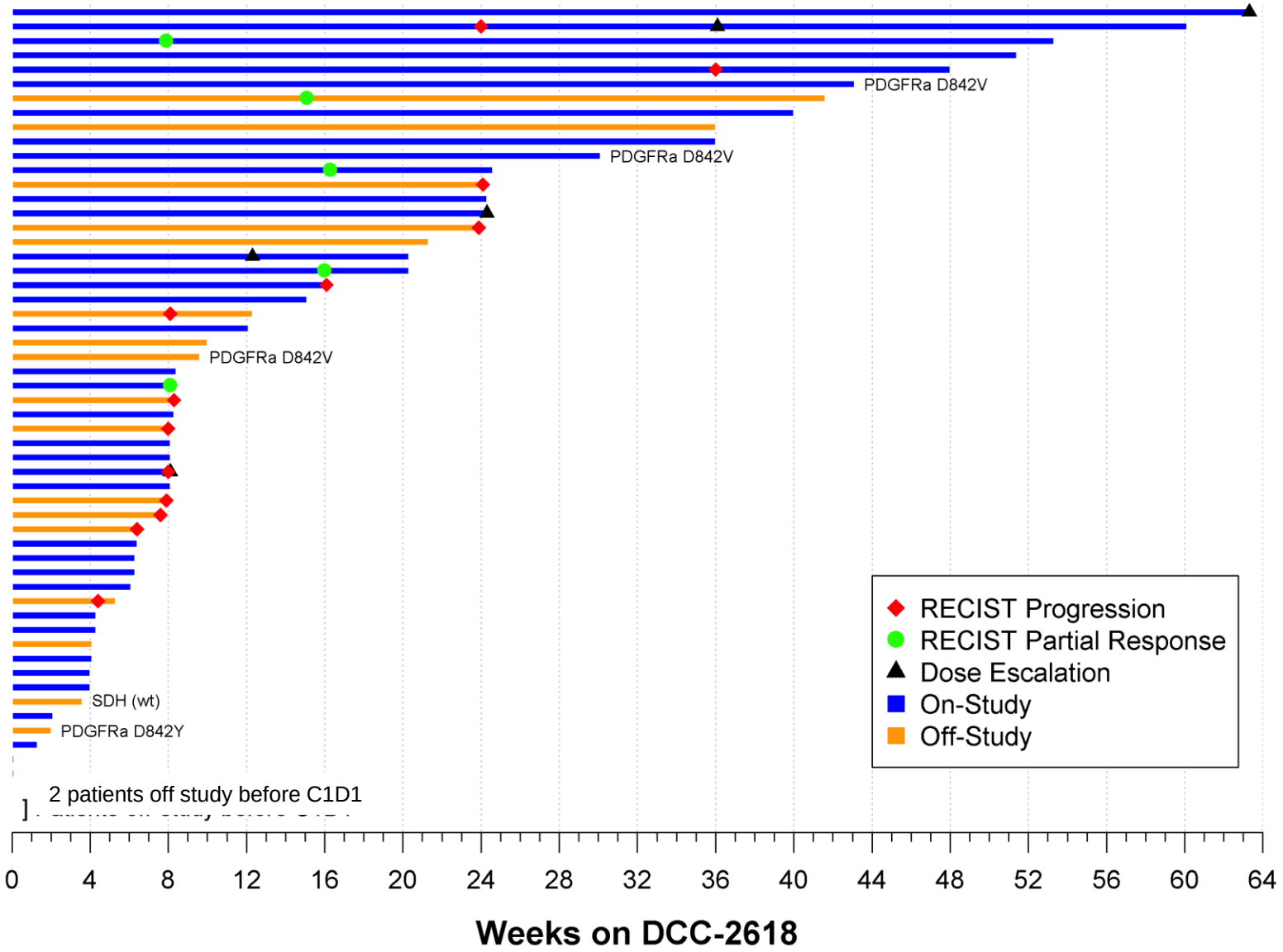
[$]One subject has a "Decreased appetite" AE with no severity grade. This is included in the total events column but nowhere else
[#]One subject has a "Dyspnoea" AE that resulted in death (G 5). This is included in the G3/4 column for the ≥ 100 mg/d group
*Unconjugated bilirubin, both patients are homozygous for 28 *(TA)7/(TA)7 UGT1A1 polymorphism

DCC-2618 – GIST Patient Characteristics (N=57)

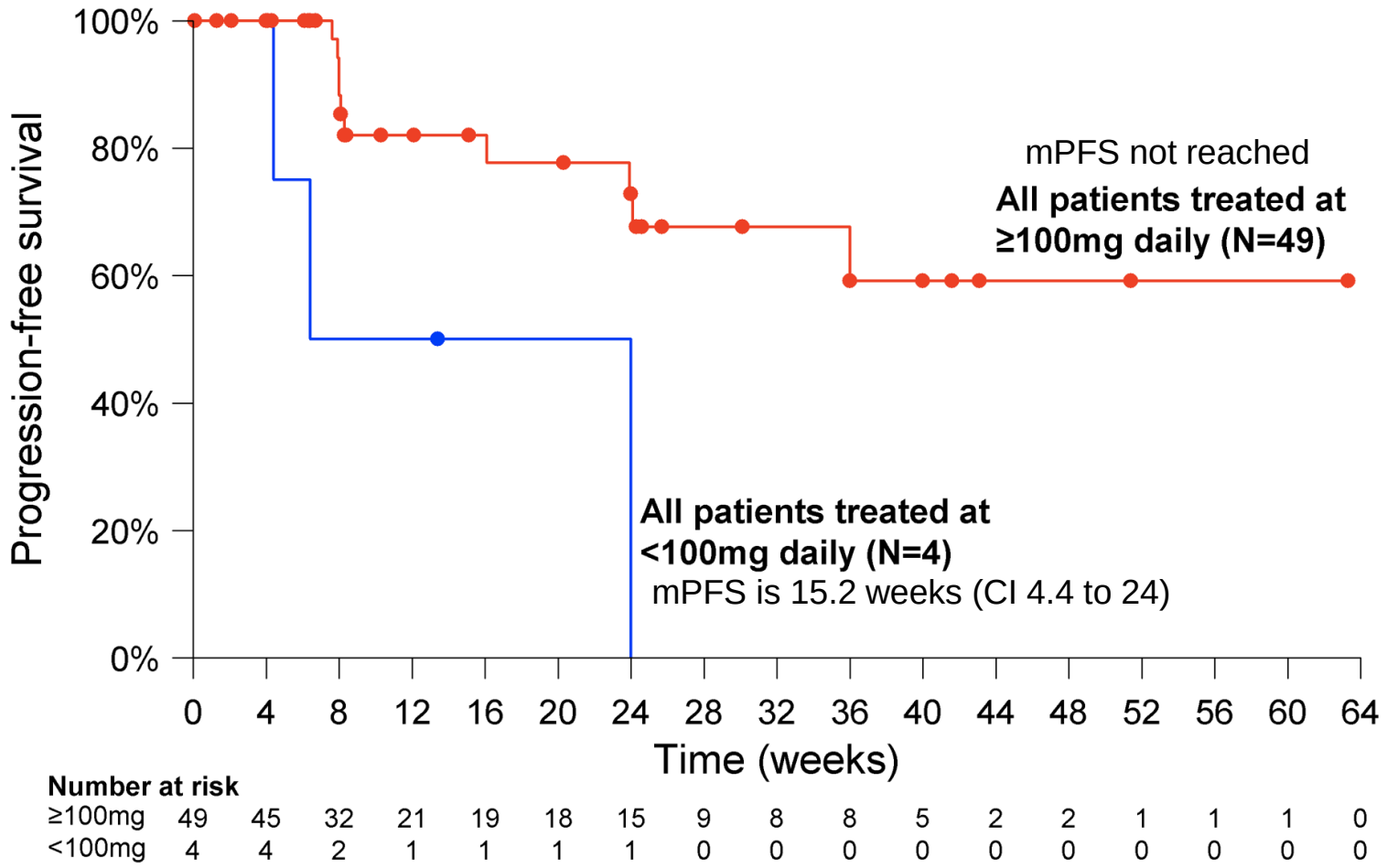
- Median age: 62 years (range 28 - 85)
- ECOG PS:
  - 0: 18 (33%)
  - 1: 37 (67%) [Note: 2 subjects missing screening ECOG]
- Baseline mutations: (archival tissue*, N=57)
  - KIT Exon 9: 13
  - KIT Exon 11: 27
  - KIT Exon 17: 4
  - PDGRα Exon18: 4
  - Other/UKN: 9 (2x KIT Ex13, 1x KIT UKN, 1x SDH, 5x not done)
- Mean prior number of agents: 3.3 (median 3; range 1 - 7)
  - Imatinib: 49/49 (100%)
  - Sunitinib: 43/49 (88%)
  - Regorafenib: 36/49 (73%)
  - Other: 35/49 (71%)
- DCC-2618 treatment doses:
  - <100 mg/day: 5 (9%)
  - ≥100 mg/day: 52 (91%)
  - **150 mg QD: 21 (37%)**

*various methods used per institutional standards

Duration of Treatment on DCC-2618 – All GIST Patients (N=57)

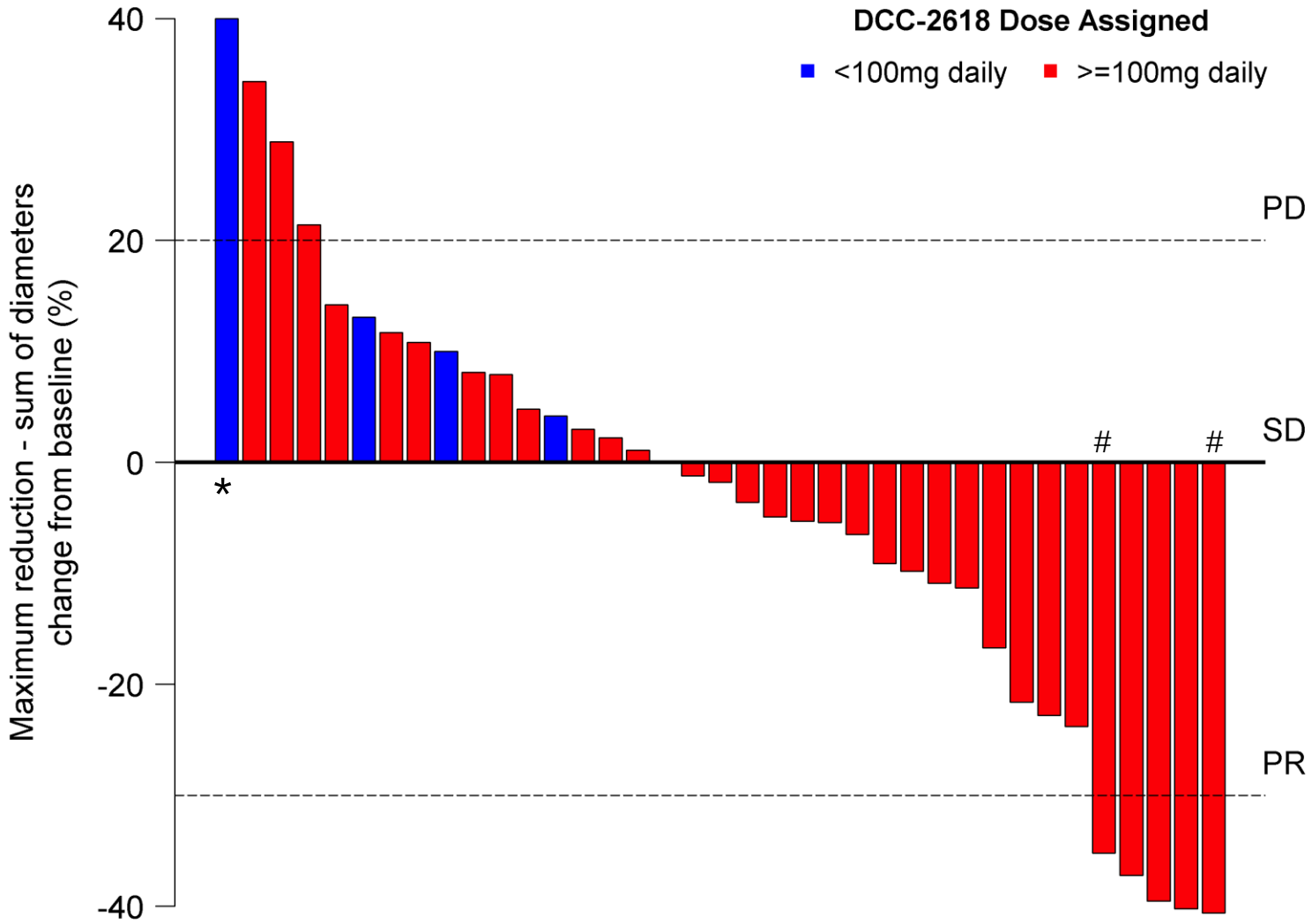


DCC-2618: Progression-Free Survival
Patients treated at ≥100 mg/d compared to <100 mg/d



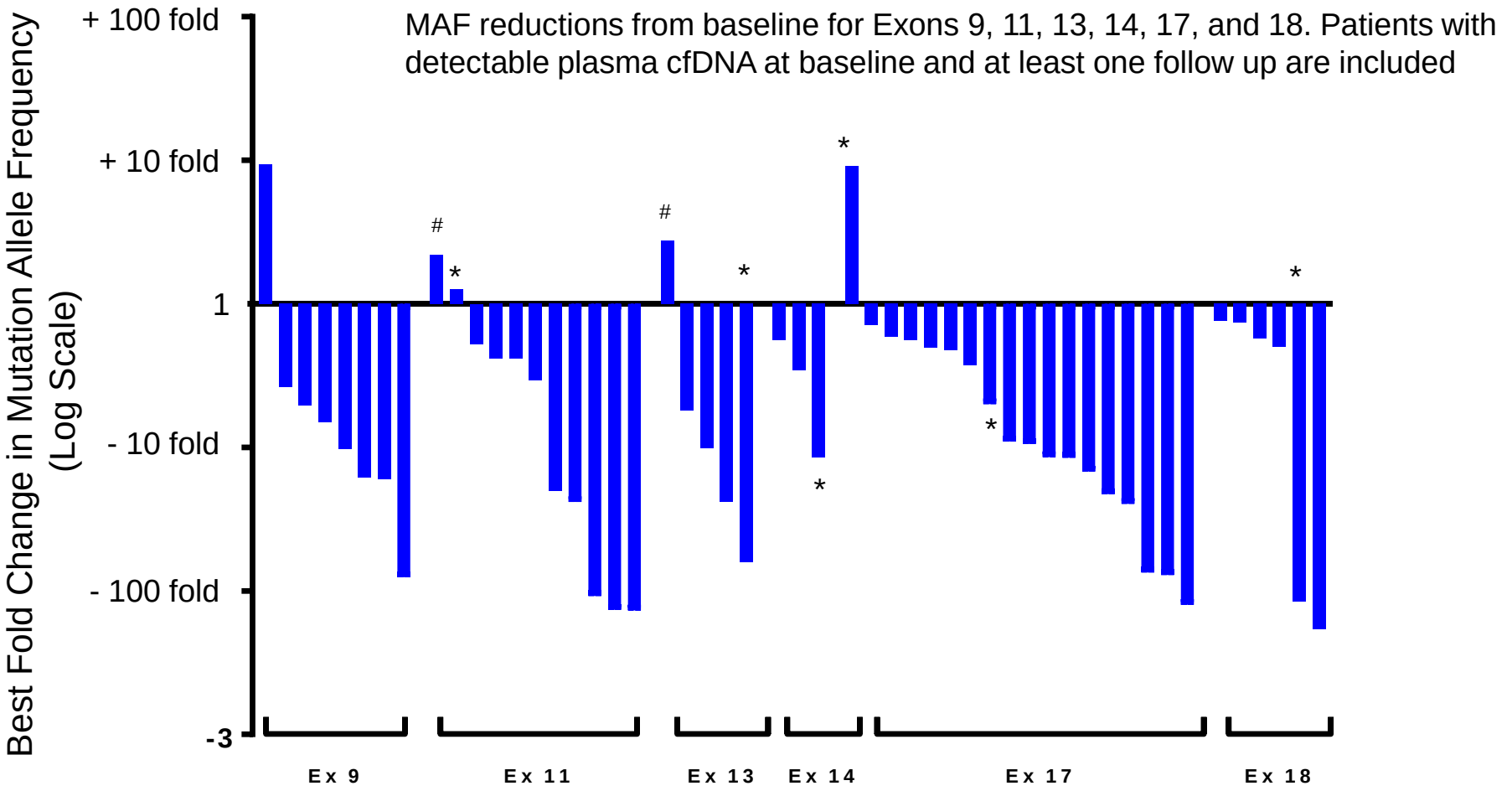
- Despite small sample size results suggest that doses of 40 or 60 mg/d are insufficient
- The fact that 30 mg BID is an insufficient dose is supported by improvement in disease control in a patient with PD after 24 weeks following dose escalation (not shown)

Waterfall Plot of KIT/PDGFRα GIST Patients (Best Response Per RECIST, N=37)



PD = Progressive disease, SD = Stable disease, PR = Partial response
*66% increase in tumor size; #PR at RP2D

Use of cfDNA as Pharmacodynamic Biomarker Demonstrates pan−KIT Activity of DCC-2618 in KIT mutant, advanced GIST Patients (Best Response, N=19)



- Enrolled patient population reveals broad range of KIT mutations
- DCC-2618 leads to reductions in MAF in cfDNA across all exons associated with resistance
- Treatment decisions were made based on disease control and not on changes in MAF

#Patient in first dose cohort, *Patient represented with mixed histology

NGS of KIT in DNA Derived From Tumor vs cfDNA (N=12)

Tumor biopsies were taken at baseline

Tumor	Plasma
KIT Ex9 Indel	KIT Ex9 Indel
KIT Ex11 W557R KIT Ex17 Y823D	KIT Ex11 W557R KIT Ex17 Y823D
KIT Ex9 Indel	KIT Ex9 Indel KIT Ex17 N822T; D820E
KIT Ex9 Indel	KIT Ex9 Indel KIT Ex11 P573S KIT Ex17 D820N KIT Ex18 S840N
KIT Ex11 V560D KIT Ex18 A829P	KIT Ex18 A829P
KIT Ex9 Indel	None

Tumor	Plasma
KIT Ex11 Indel KIT Ex13 V654A KIT Ex17 Y823D	KIT Ex11 Indel KIT Ex13 V654A KIT Ex14 N680K KIT Ex17 Y823D; Y823C; Indel
KIT Ex11 V560D KIT Ex17 D820Y	KIT Ex11 V560D KIT Ex17 D820Y
KIT Ex11 Indel KIT Ex18 A829P	KIT Ex11 Indel KIT Ex13 V654A KIT Ex14 N680K KIT Ex17 D820G; V824M KIT Ex18 A829P
*KIT Ex11 Indel KIT Ex13 V654A KIT Ex17 Y823D	*None
None	None
KIT Ex11 Indel	None

- Tumor tissue detected in 23/28 patients with available biopsies at baseline
  - 12/23 samples passed required quality for NGS
- Baseline molecular characteristics reveal broad diversity of KIT mutations in both tumor and plasma sample
- More resistance mutations were found in plasma cfDNA compared to tissue biopsies

*Patient changed treatment due to toxicity and not progressive disease

DCC-2618 Expansion Study of Phase 1 Study

- Three cohorts for KIT or PDGFRa mutant GIST patients who progressed on imatinib or are intolerant
  - Second and third line patients
  - 4th line patients
  - 5th line patients
- Multiple US sites and Toronto open
  - European sites to open starting in November
- Study objective is to further evaluate the safety and tolerability of oral DCC-2618 at 150 mg QD and to determine its antitumor activity
- ClinicalTrials.gov Identifier: NCT02571036

Conclusions

- DCC-2618 was well tolerated up to doses of 200 mg BID
- DCC-2618 shows encouraging disease control in heavily pre-treated GIST patients
  - The DCR for KIT- and PDGFRα mutant GIST for cohorts receiving total daily dose of ≥100 mg is 76% (19/25) at 12 weeks and 57% (12/21) at 24 weeks
- Breadth of mutations observed in patients at baseline demonstrates the need for a therapy able to inhibit the full spectrum of mutant KIT
  - The cfDNA MAF reduction across all exons supports the pan−KIT activity of DCC-2618
  - Results from 12 patients, while preliminary for concordance, favor use of liquid biopsies over tissue biopsies
- The encouraging results strongly support testing of DCC-2618 in the planned placebo-controlled randomized, pivotal phase 3 study in patients who have received at least 3 prior agents (invictus)

invictus Study – Participating Countries

The countries that will be involved in invictus are:

- North America: US, Canada
- Europe: Belgium, Finland, France, Germany, Italy, Netherlands, Poland, Spain, UK
- Australia
- Singapore

Summary

- New KIT/PDGFRa directed therapies which have demonstrated promising activity in advanced GIST particularly in PDGFRa D842V and KIT mutant tumors

- International pivotal Phase 3s trials hold promise to further these opportunities to study new drugs in GIST