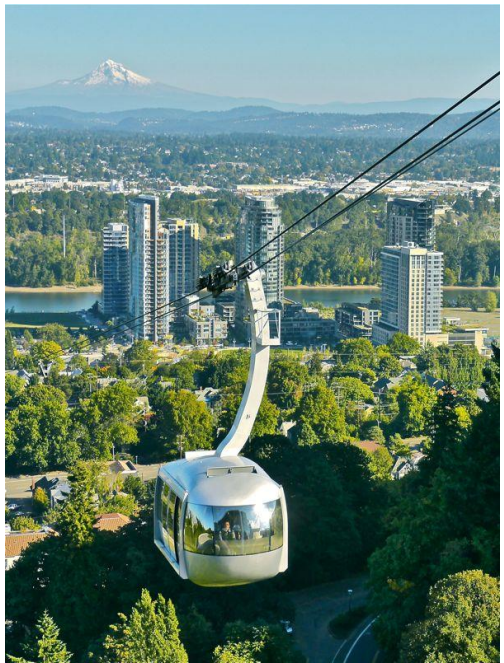
New Drugs to Treat GIST: An update on ongoing clinical studies

Michael Heinrich, M.D.



OHSU
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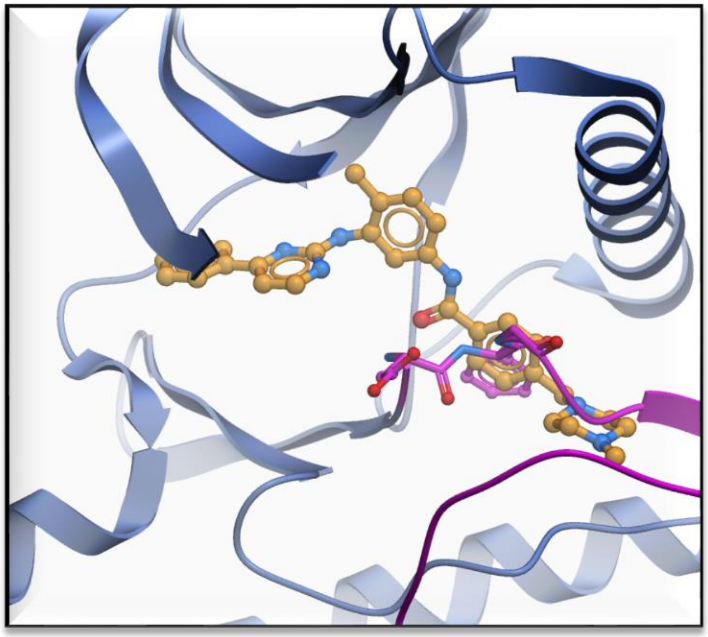
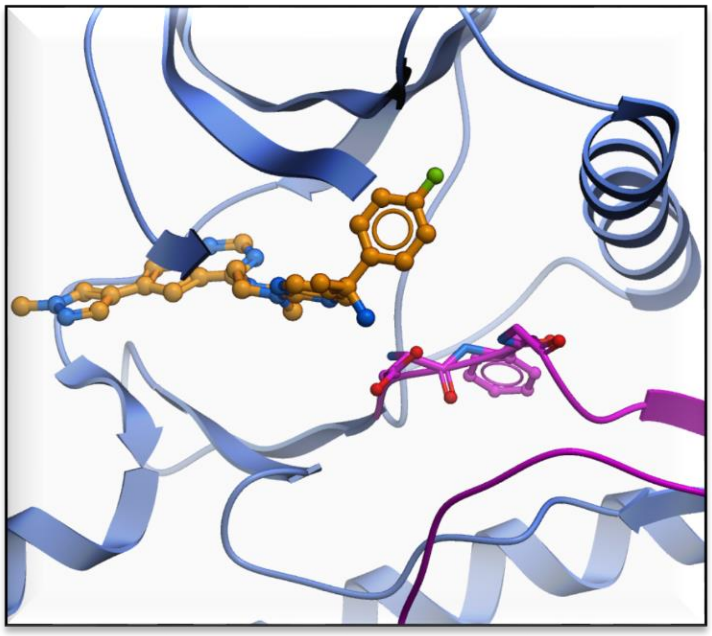
New Agents in GIST

- Avapritinib (BLU-285) and DCC-2618
- Both are novel potent and specific KIT inhibitors that were rationally designed to inhibit TKI-resistance mutations associated with drug-resistant GIST
- Both have completed phase 1 dose escalation dose expansion studies for advanced GIST

Avapritinib (BLU-285) is a potent type 1 KIT/PDGFRα inhibitor that binds to the active conformation of the kinase

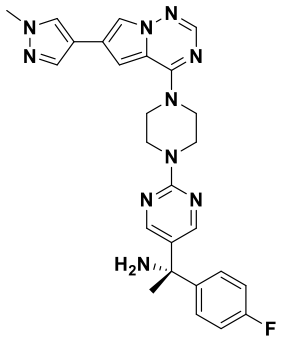


Imatinib
Activation loop open



BLU-285
Activation loop open

BLU-285



NAVIGATOR
Avapritinib Phase 1 Study Design

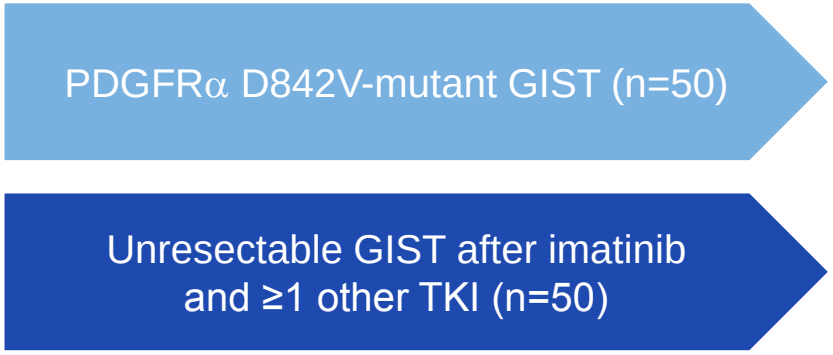
Key objectives

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

Part 1
Dose escalation *completed*

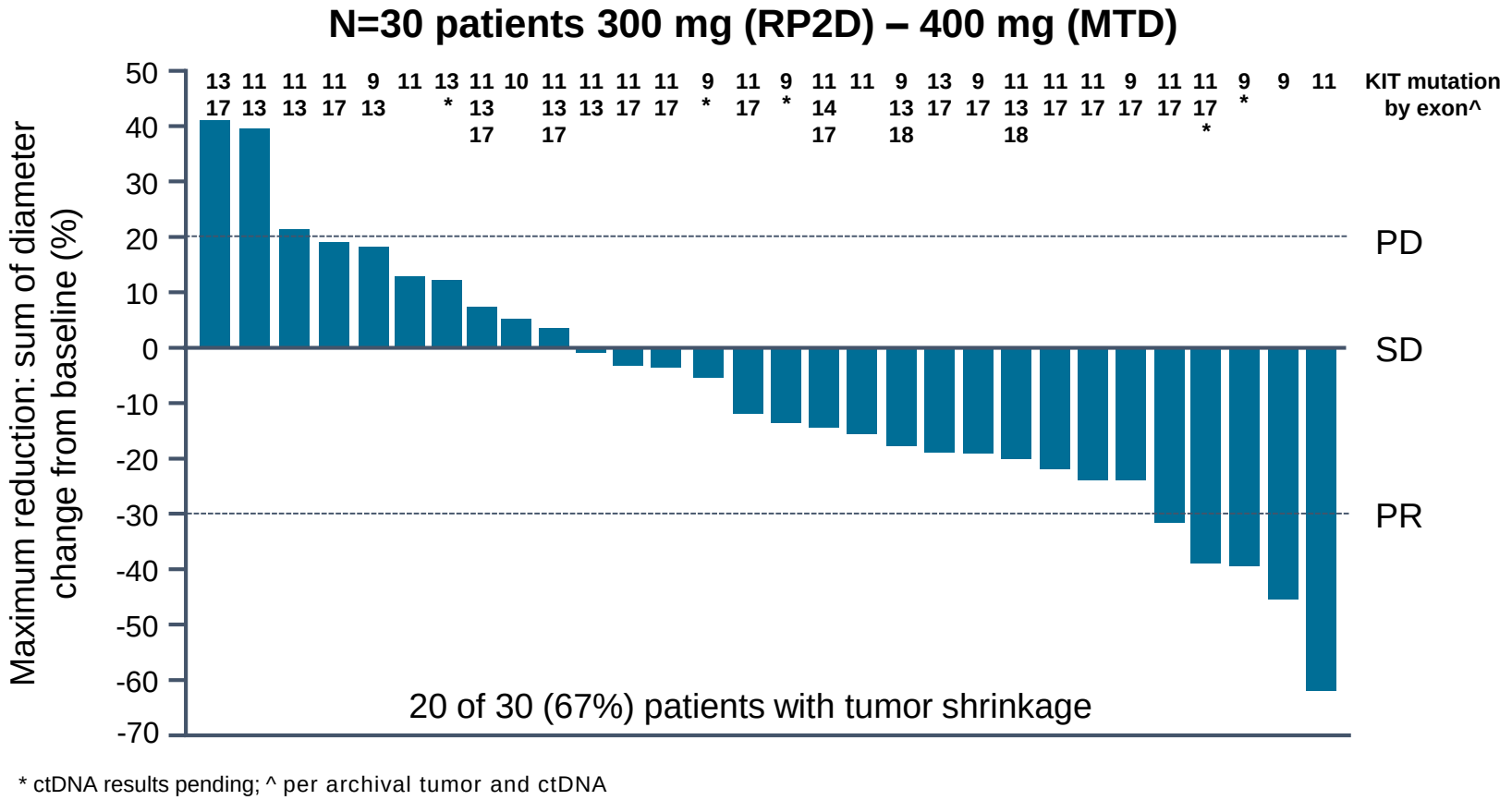
- 3+3 design with enrichment
- Dose levels: 30, 60, 90, 135, 200, 300, 400 and 600 mg QD
- MTD determined to be 400 mg PO QD

Part 2
Dose expansion *enrolling*



Avapritinib phase 1-2 Study

Tumor reduction across multiple KIT genotypes (central radiology review)



* ctDNA results pending; ^ per archival tumor and ctDNA

Heinrich et al, CTOS 2017

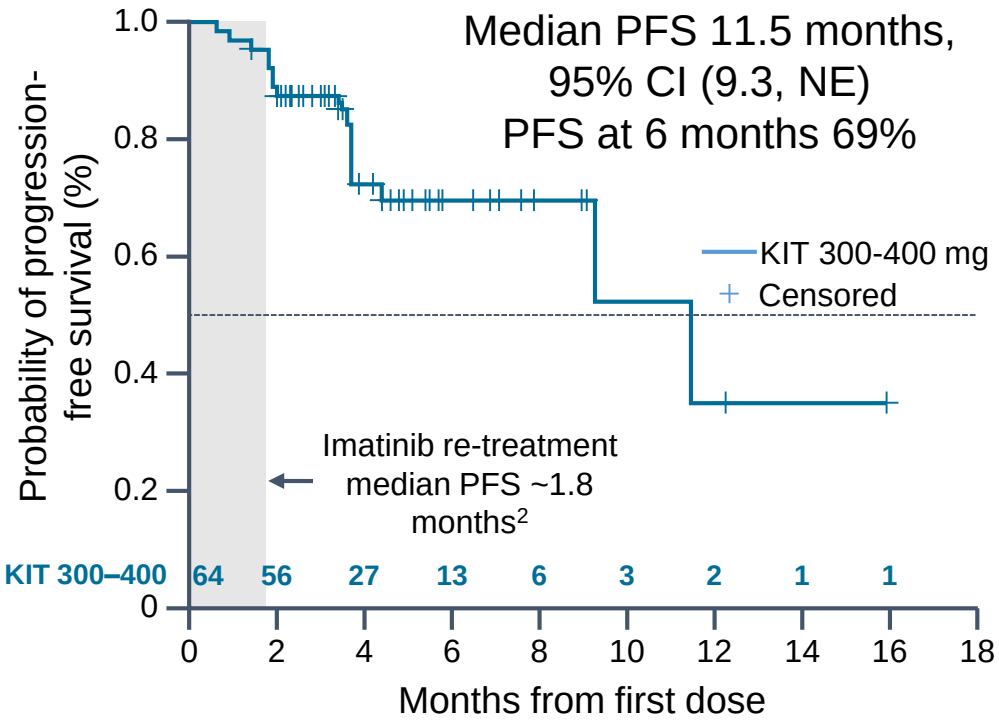
Avapritinib phase 1-2 Study

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

- 35 of 64 patients remain on therapy
- No approved therapies beyond third-line regorafenib
  - ORR ~0% with imatinib re-treatment in ≥third-line[2]

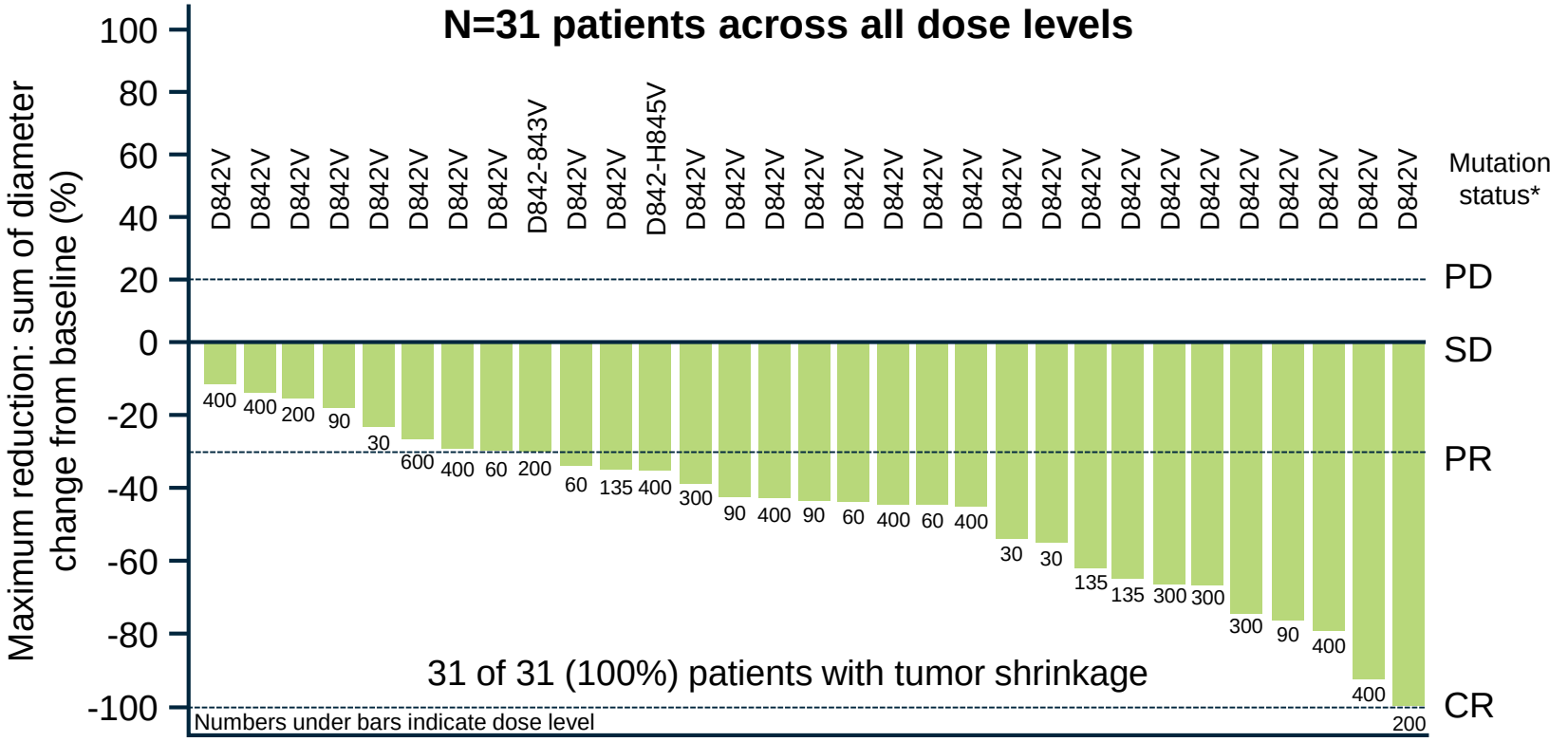


2. Kang et al. Lancet Oncol. 2013;14(12):1175–82

Heinrich et al, CTOS 2017

Avapritinib phase 1-2 Study

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



* per archival tumor and ctDNA

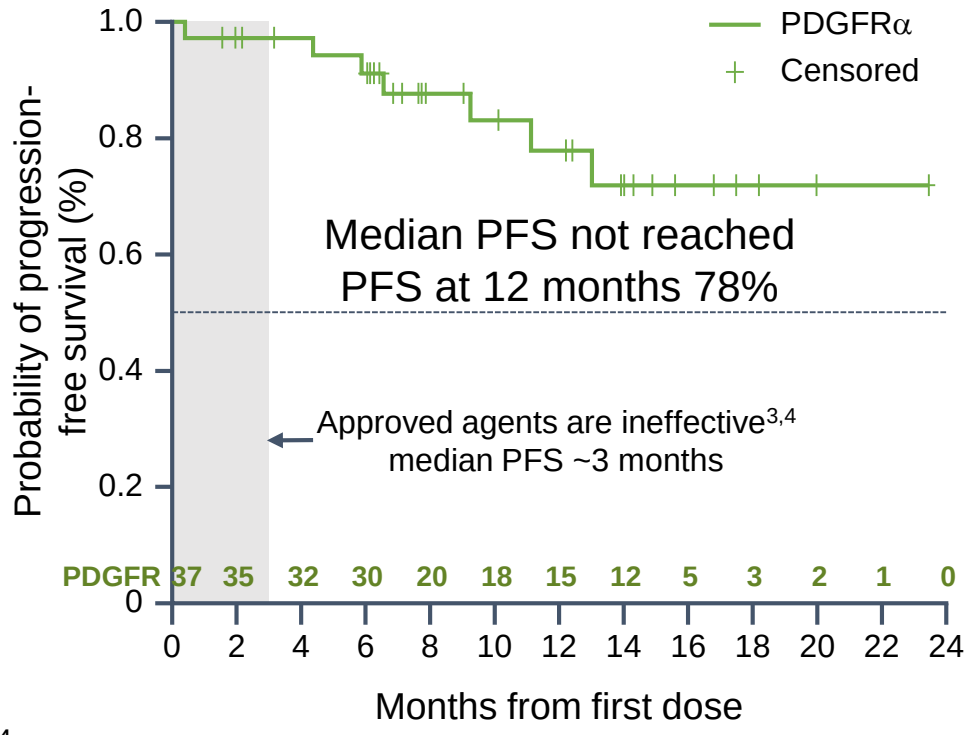
Heinrich et al, CTOS 2017

Avapritinib phase 1-2 Study

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



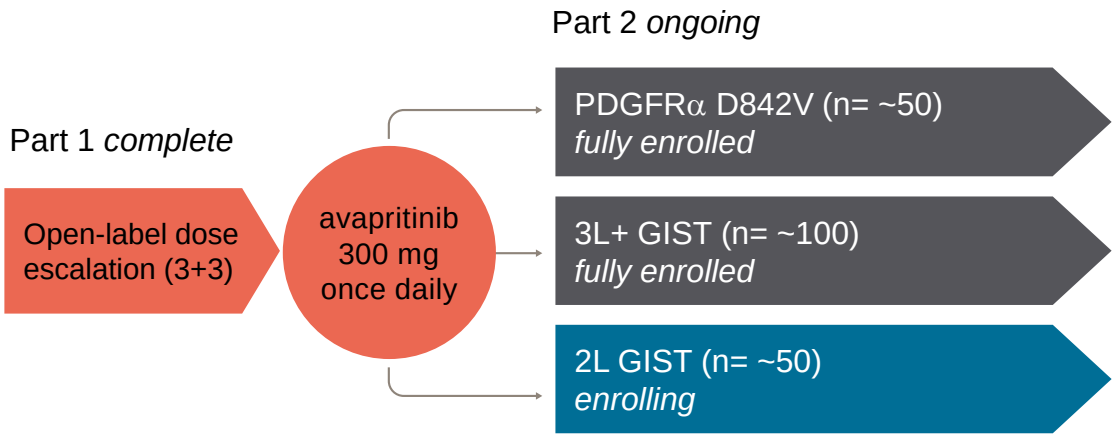
- 30 of 37 remain on therapy
- ORR ~0% with currently approved agents[3,4]

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

Heinrich et al, CTOS 2017

Phase 1 NAVIGATOR clinical trial now enrolling patients with 2L GIST

NAVIGATOR GIST



Key endpoints: overall response rate, duration of response, safety

Design

- Open-label, Phase 1 clinical trial
- All enrolled patients receive avapritinib

Eligibility

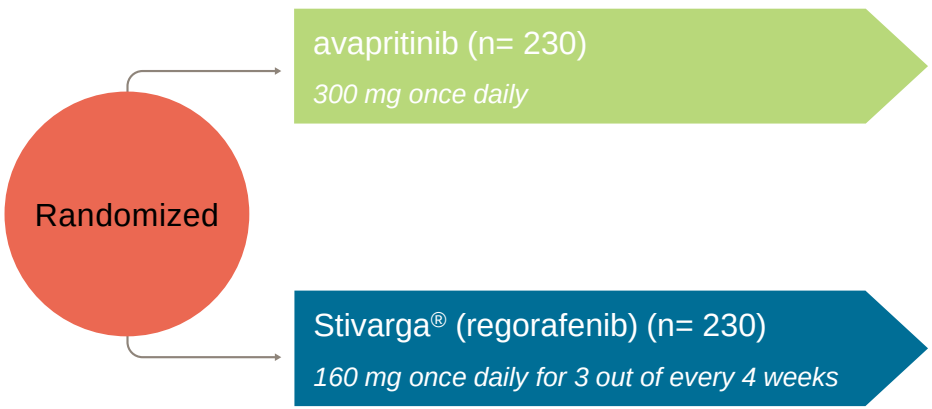
- Aged 18 years or older
- Metastatic and/or unresectable GIST
- Have received Gleevec® (imatinib) or are intolerant to imatinib

More Information

- Website: www.NavigatorStudy.com
- Email: studydirector@blueprintmedicines.com

Phase 3 VOYAGER is now enrolling patients with 3L and 4L GIST

VOYAGER GIST



Primary endpoint: progression free survival

Design

- Open-label, randomized, Phase 3 clinical trial
- Patients randomized to receive either avapritinib or Stivarga® (regorafenib)
- Patients assigned to receive regorafenib may cross over to receive avapritinib following confirmed disease progression

Eligibility

- Aged 18 years or older
- Metastatic and/or unresectable GIST
- Have received Gleevec® (imatinib) and 1 or 2 other tyrosine kinase inhibitors

More Information

- Website: www.VoyagerTrial.com
- Email: studydirector@blueprintmedicines.com

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 MD Anderson Cancer Center
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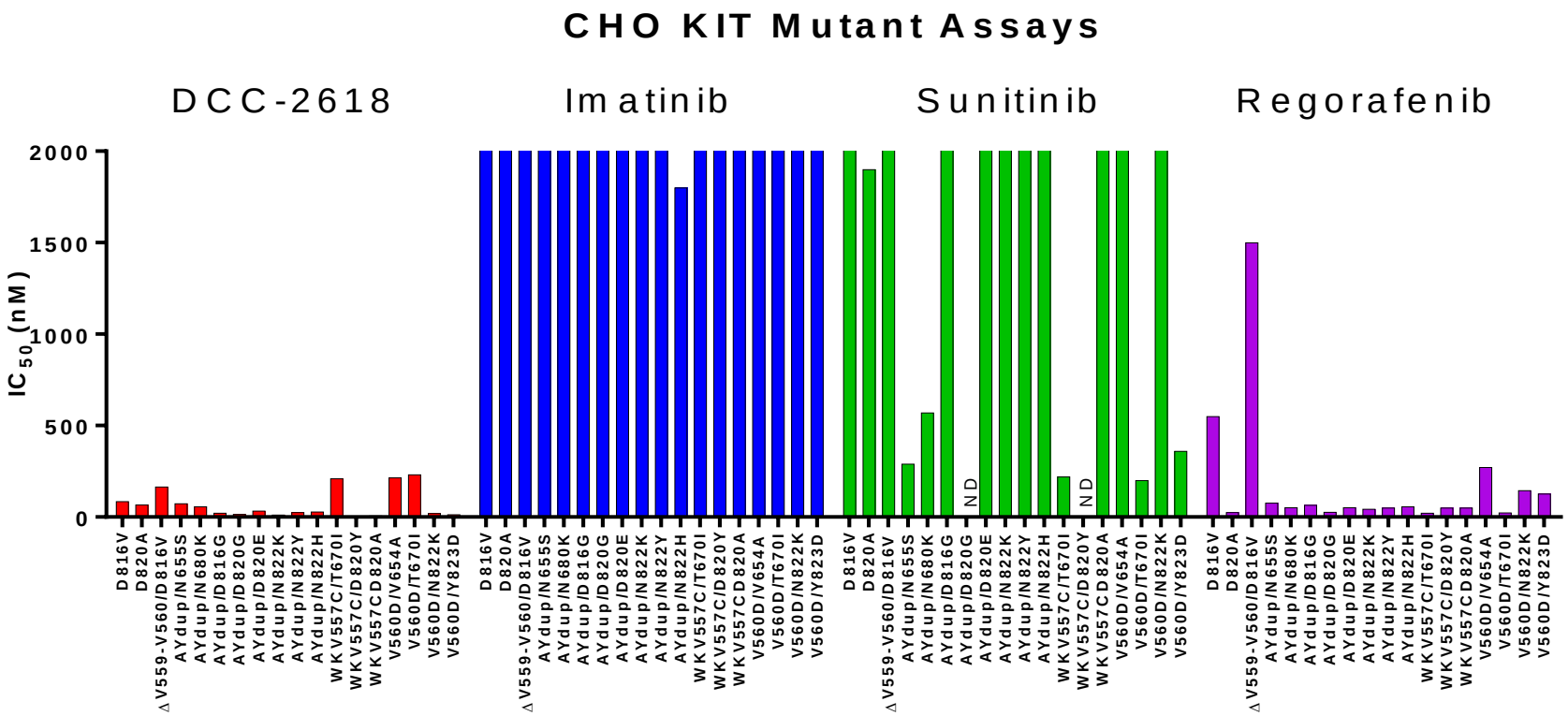
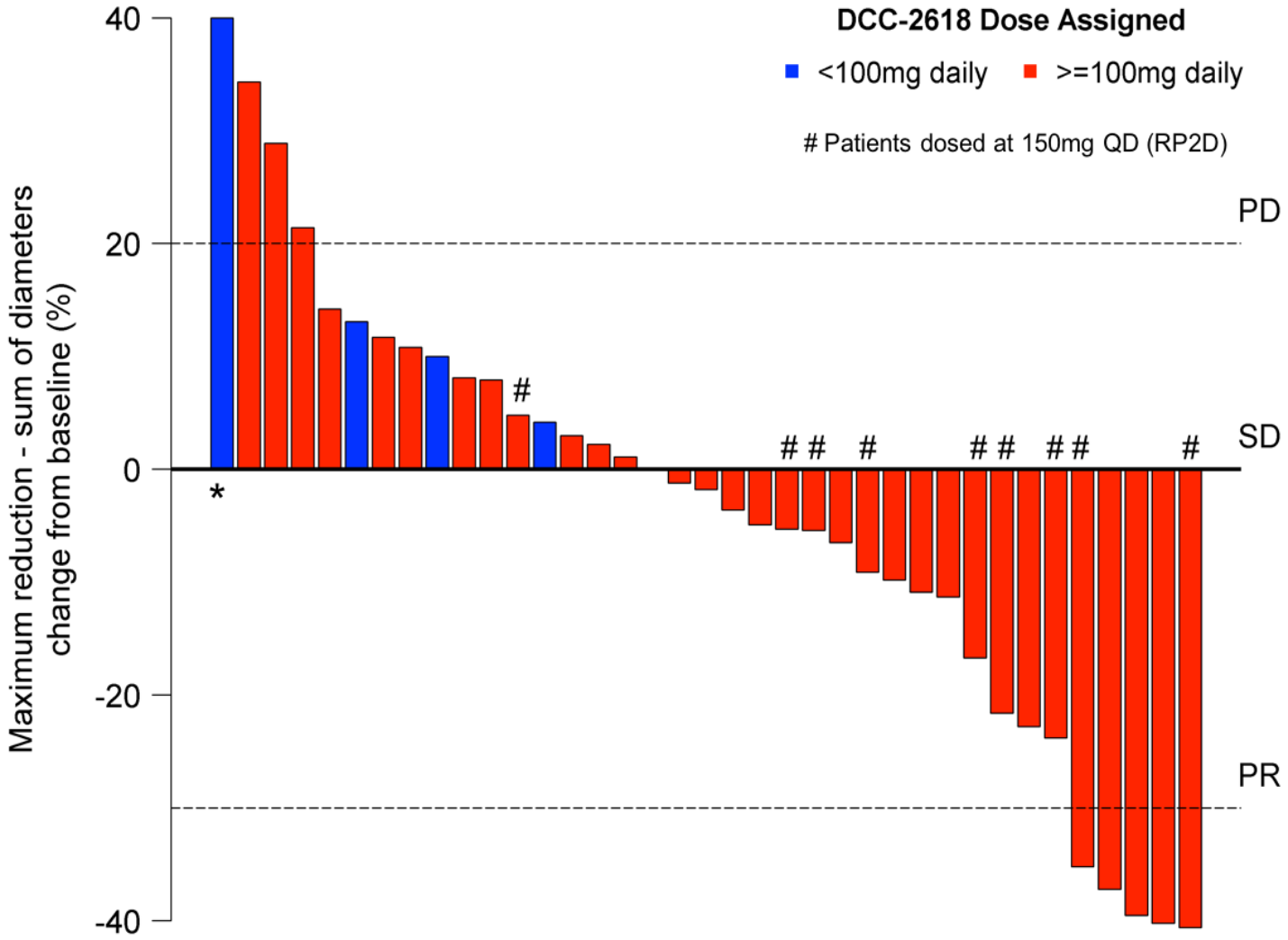
RATIONALE FOR DCC-2618 STUDY

- 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



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

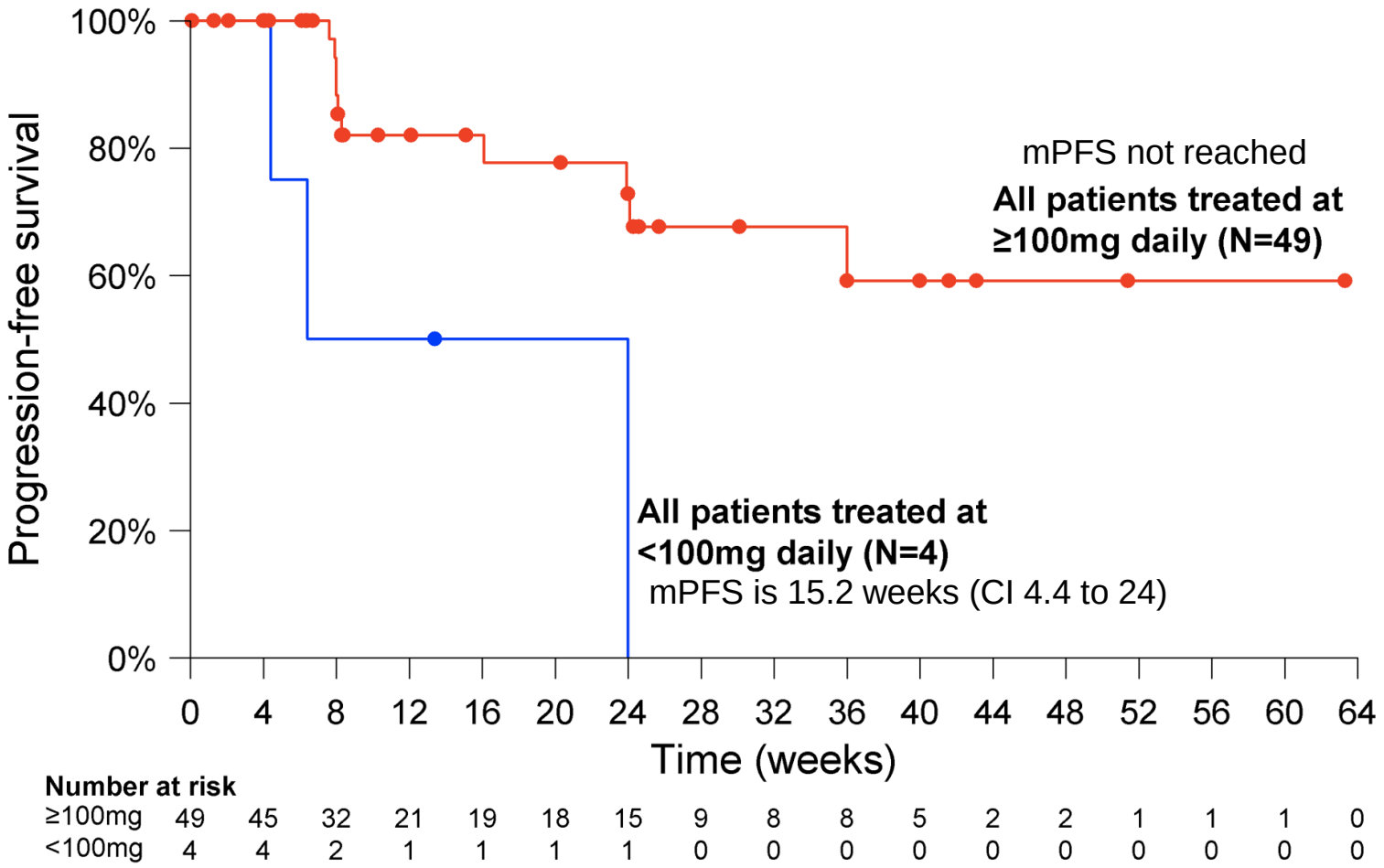


PD = Progressive disease, SD = Stable disease, PR = Partial response

*66% increase in tumor size; #Patients treated at RP2D

DCC-2618: Progression-Free Survival

Patients treated at ≥100 mg/d compared to <100 mg/d

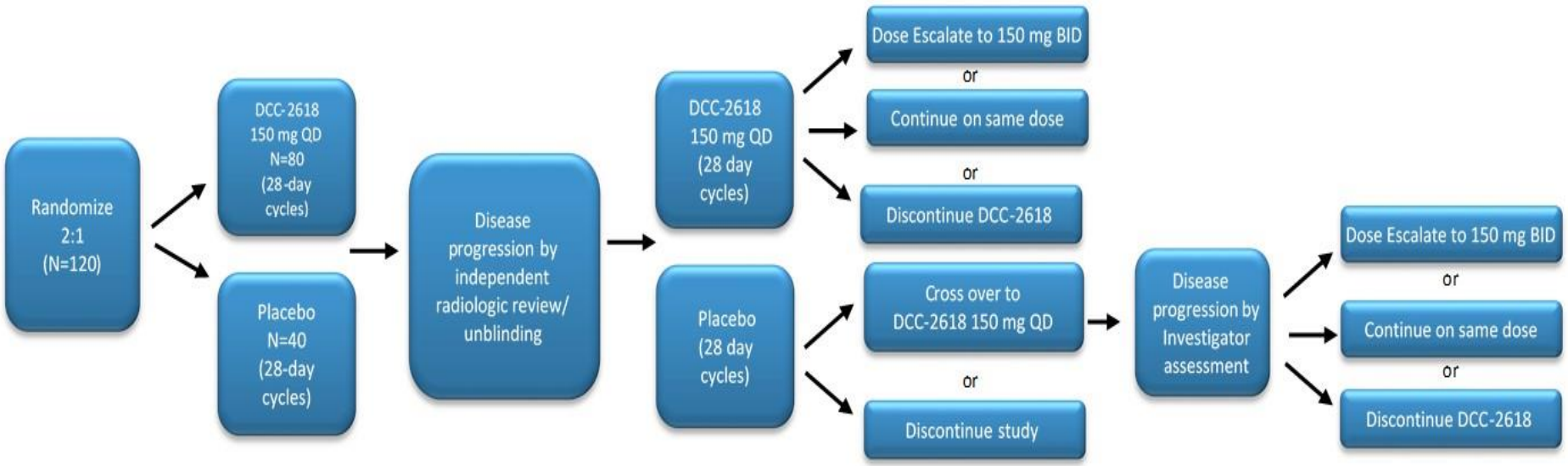


- Despite small sample size results suggest that doses of 40 or 60 mg/d are insufficient
- The fact that 30 mg BID is an insufficient dose is supported by improvement in disease control in a patient with PD after 24 weeks following dose escalation (not shown)

invictus Study - Phase 3 Trial Design

invictus

A Phase 3, INterVentional, Double-Blind Study to Assess Safety and Efficacy of DCC-2618 In Patients with Advanced c-KIT/PDGFRA Gastrointestinal Stromal TUmorS Who Have Received Prior Treatment with Imatinib, Sunitinib, and Regorafenib



Primary endpoint PFS

Planned to complete enrollment in October 2018

invictus

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

Planned intrigue Study

Phase 3 Pivotal Trial of DCC-2618 versus sunitinib

FPI 2H 2018

deciphera

intrigue

- The primary endpoint in this pivotal Phase 3 trial in second-line GIST will most likely be a clinically meaningful improvement in median PFS in patients treated with DCC-2618 compared to sunitinib.
- Median PFS will be determined by independent radiologic review of CT scans, as assessed by RECIST
- In this pivotal Phase 3 trial in second-line GIST, we expect to enroll patients who have progressed on or are intolerant to imatinib, comparing DCC-2618 against sunitinib.
- The design for this trial has not yet been finalized

Summary of Clinical Development of New Agents in GIST

- Avapritinib will be tested in a phase 3 randomized, open-label study vs. third-line regorafenib (VOYAGER, now open at a few sites, the rest to be opened by November, 2018)
- Based on the phase 1-2 data, Blueprint Medicines is seeking approval of avapritinib for treatment of D842V-mutant GIST
- DCC-2618 is currently being tested in a phase 3 randomized, double-blind, placebo-controlled study of treatment of advanced GIST in the fourth-line or later (invictus, open now, projected to complete enrollment by November 2018)
- DCC-2618 will also be tested in a randomized phase 3 study vs. sunitinib for second-line treatment of advanced GIST (intrigue, opening soon)

Avapritinib
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

DCC-2618
Favorable Tolerability Profile

Treatment-emergent Adverse Events in ≥ (10%) GIST Patients (n=100) @ 150 mg QD

GIST PATIENTS @ 150 mg QD			
ADVERSE EVENT	GRADE 1/2	GRADE 3/4	TOTAL (n=**100**)
Alopecia	39	0	39 (39%)
Fatigue	39	0	39 (39%)
Myalgia	35	0	35 (35%)
Constipation	29	0	29 (29%)
Hand-Foot-Skin reaction	26	1	27 (27%)
Rash	21	0	21 (21%)
Lipase increased	10	10	20 (20%)
Nausea	19	0	19 (19%)
Decreased appetite	18	0	18 (18%)
Diarrhea	16	2	18 (18%)
Hypertension	15	2	17 (17%)
Abdominal pain	14	2	16 (16%)
Arthralgia	15	0	15 (15%)
Weight decreased	13	0	13 (13%)
Headache	12	0	12 (12%)
Vomiting	12	0	12 (12%)
Anemia	8	3	11 (11%)
Dyspnea	10	1	11 (11%)
Hypomagnesaemia	11	0	11 (11%)
Pain in extremity	11	0	11 (11%)
Dry skin	10	0	10 (10%)
Muscle spasms	10	0	10 (10%)

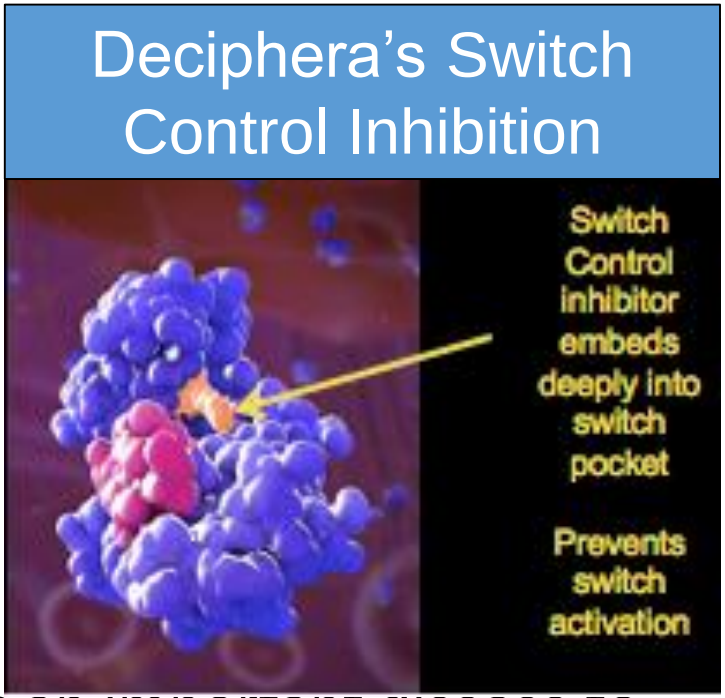
Note: Data presented at AACR Annual Meeting on April 16, 2018 based on cutoff as of March 18, 2018.

Phase 1 Dose Escalation (n=68)

- Well tolerated up to 400 mg per day
- MTD not reached
- 3 DLTs:
  - Reversible plasma enzyme elevations: lipase (2) and CPK (1)
  - Deemed not clinically significant
- 150 mg QD dose for Phase 1 Expansion and 4th Line GIST Phase 3 Trial

DCC-2618 BACKGROUND

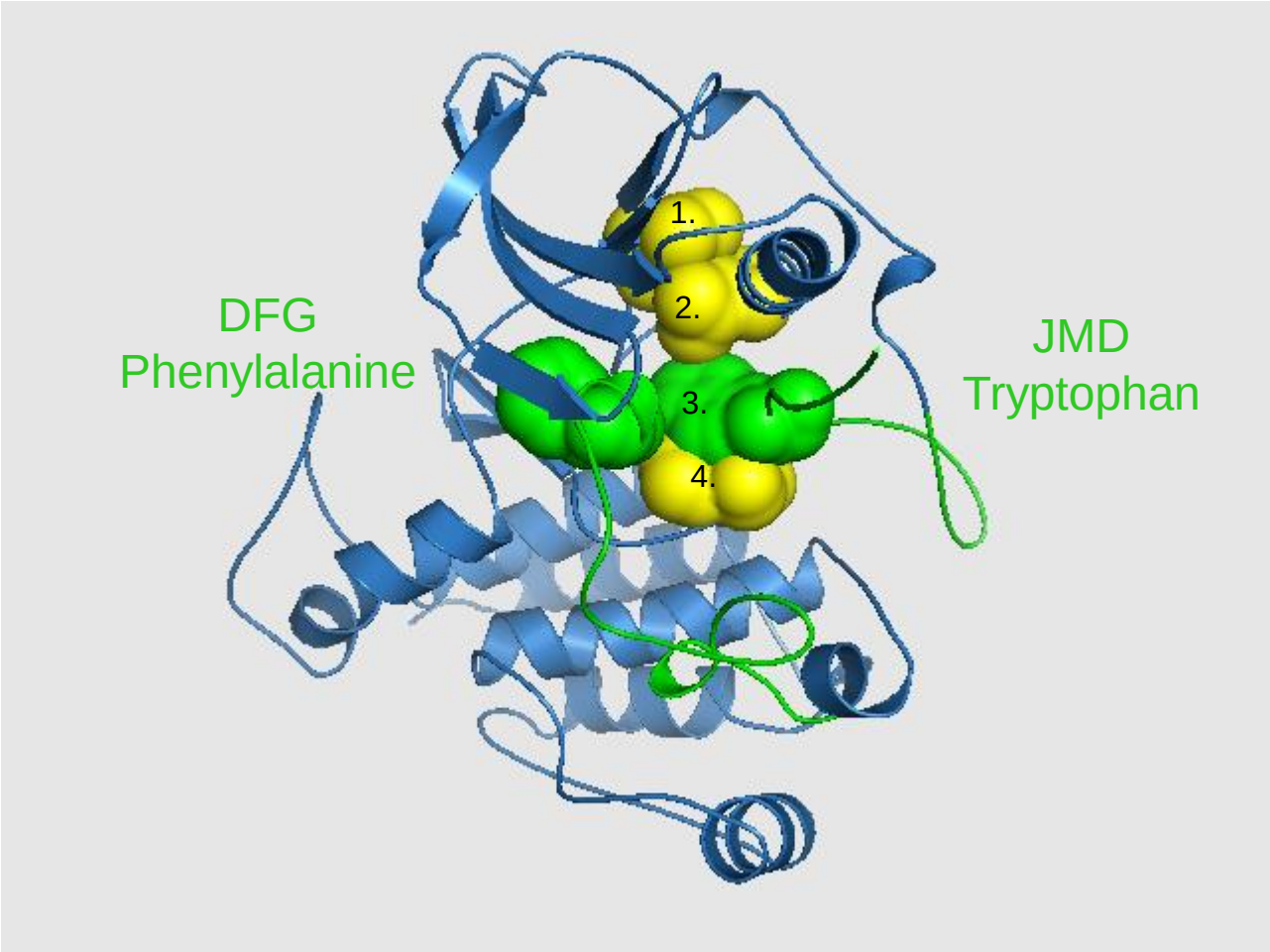
- DCC-2618 is a *KIT* and *PDGFRA* inhibitor resilient to gain-of-function and drug resistance mutations
  - Potency independent of ATP concentration



- 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*

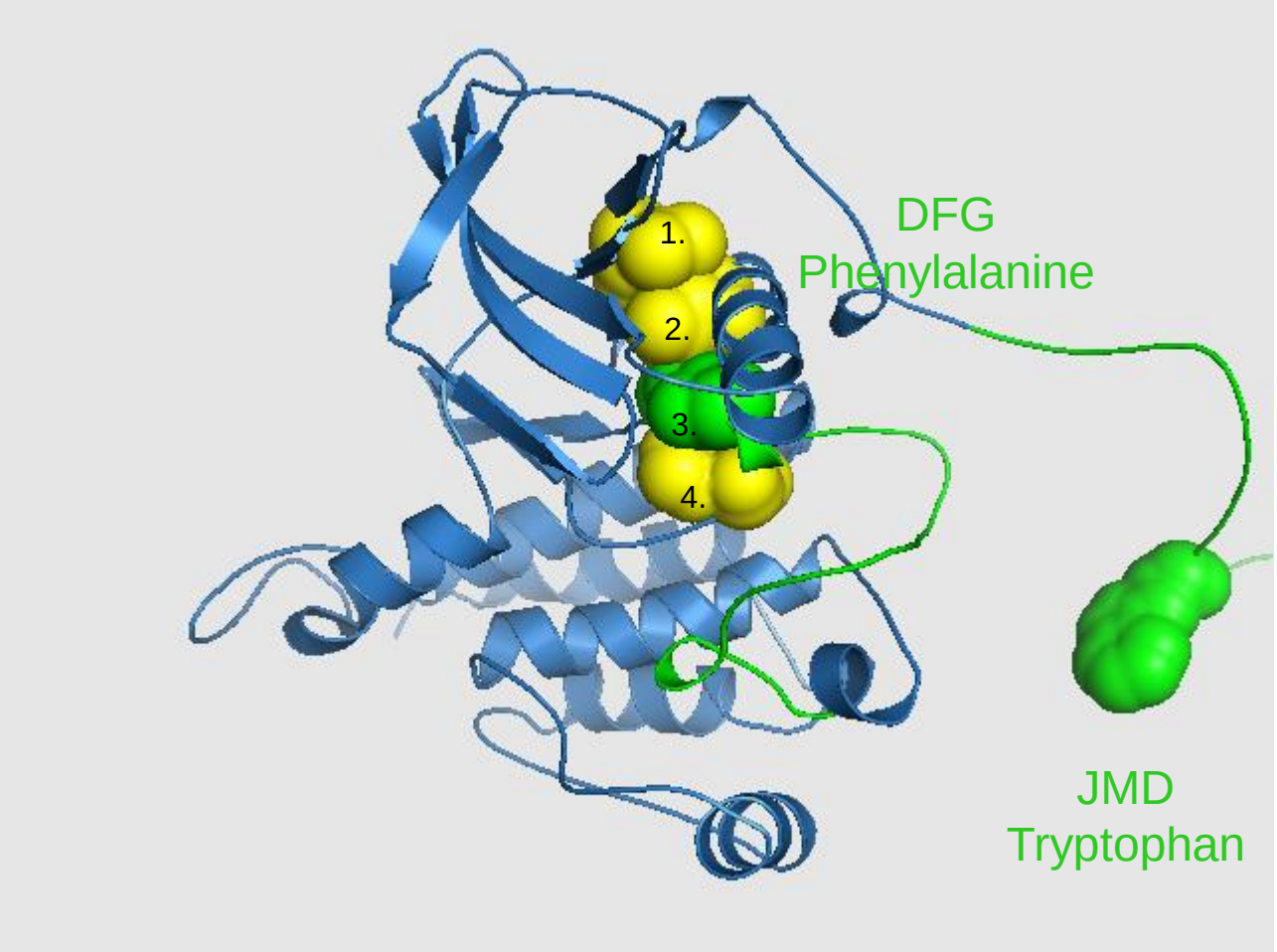
JM-Inhibited Inactive Kinase



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.

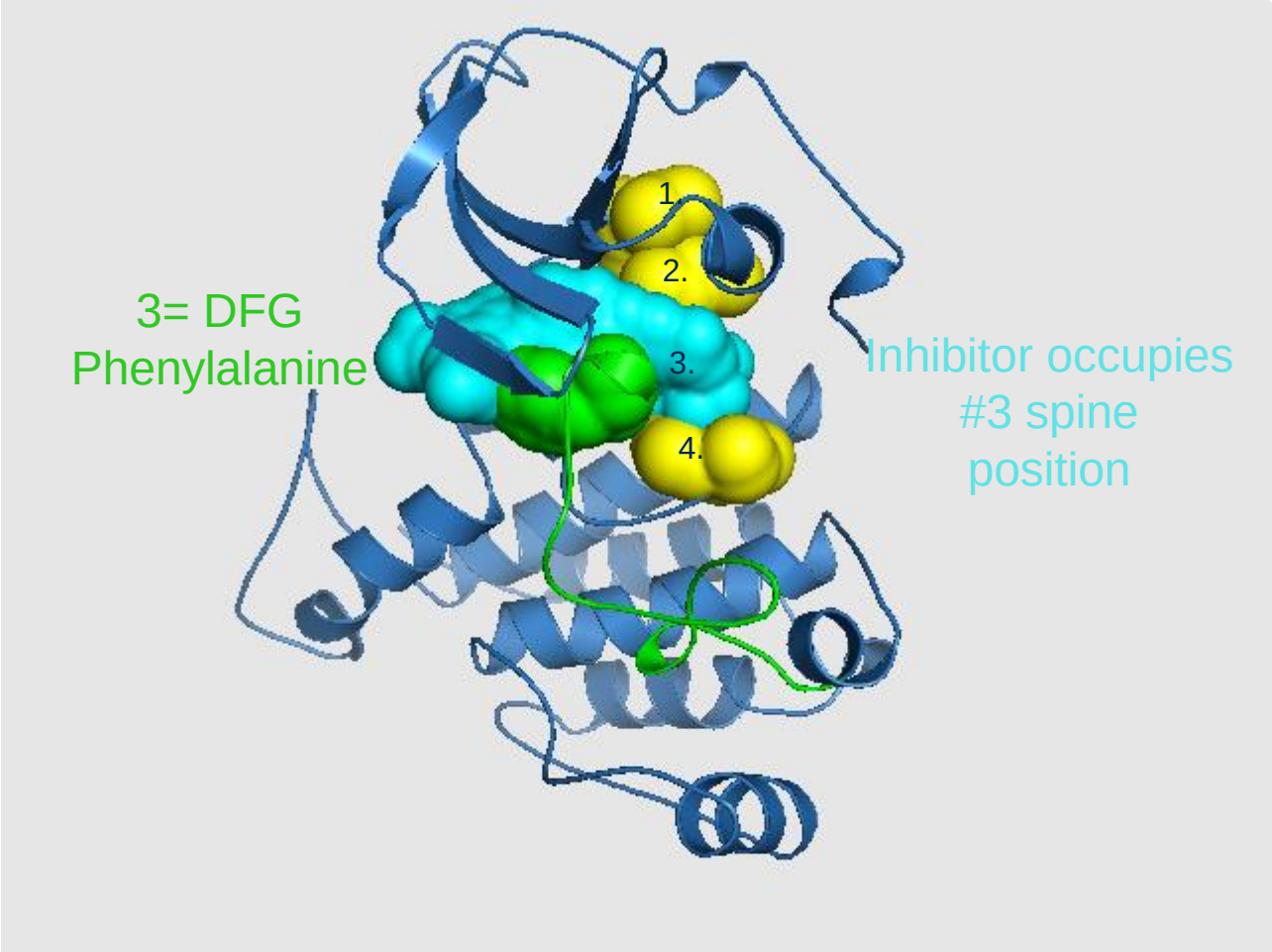
Activated Kinase Structure



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



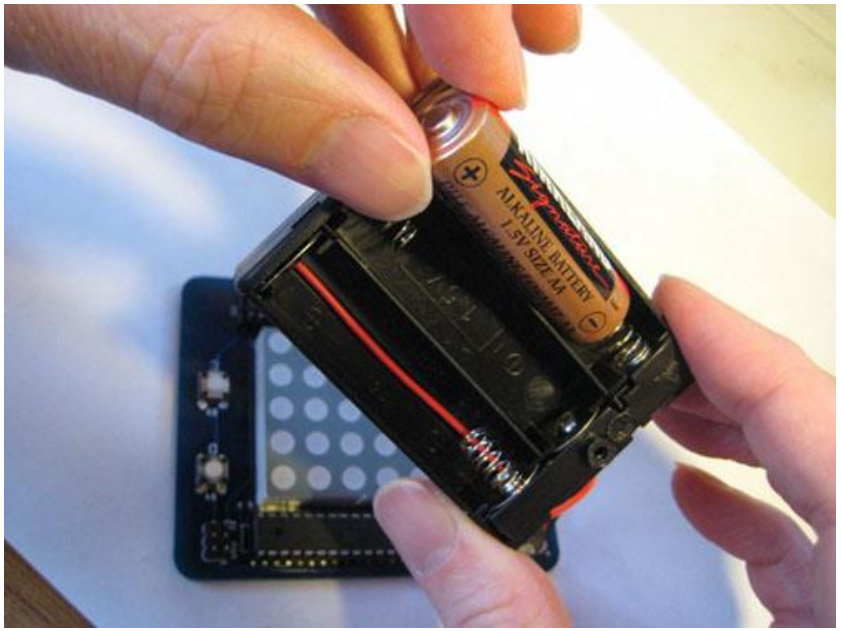
Snapshot 5. Switch Pocket Inhibitor binds to mutant KIT, with part of the inhibitor structure (blue) occupying the #3 position of the spine. This binding mode provides a biomimetic surrogate for the deleted inhibitory switch of mutant KIT.

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

Background

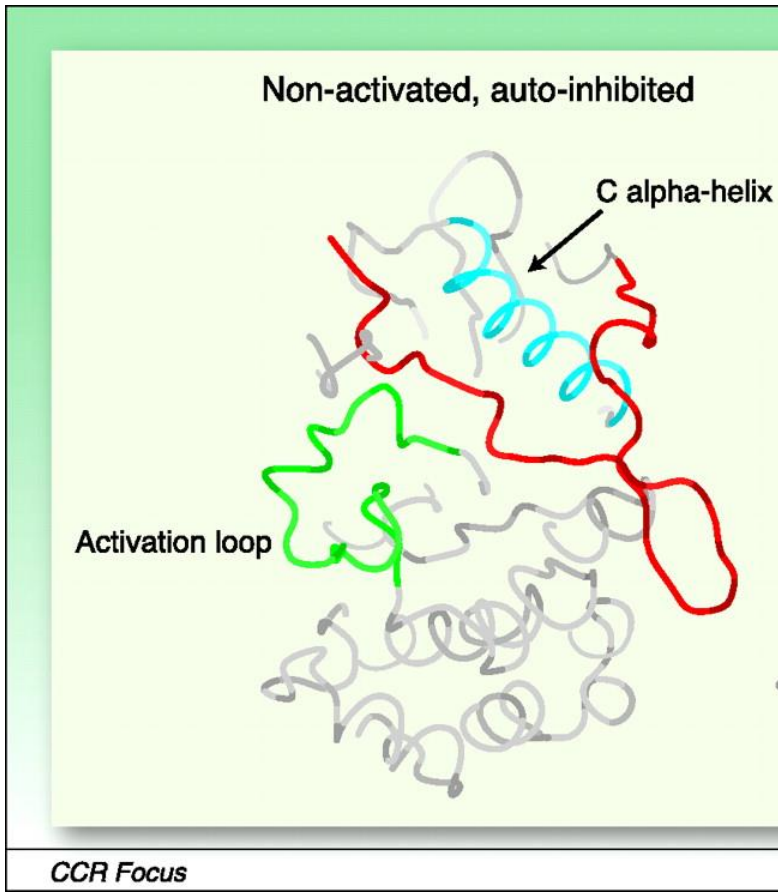
- Inhibitors of KIT/PDGFRA (TKIs) such as imatinib and sunitinib have transformed the medical treatment of advanced GIST
- However, disease control in the metastatic setting is limited by the development of drug-resistant clones
- Concept 1: To date, all approved TKIs used for the treatment of GIST are competitive ATP inhibitors
- Concept 2: To date, all approved TKIs used for the treatment of GIST bind to the inactive kinase structure
- Concept 3: Drug-resistance is commonly due to the development of acquired mutations in the disease causing mutant kinase (e.g. KIT)

Concept 1: ATP is the battery pack for KIT/PDGFRA



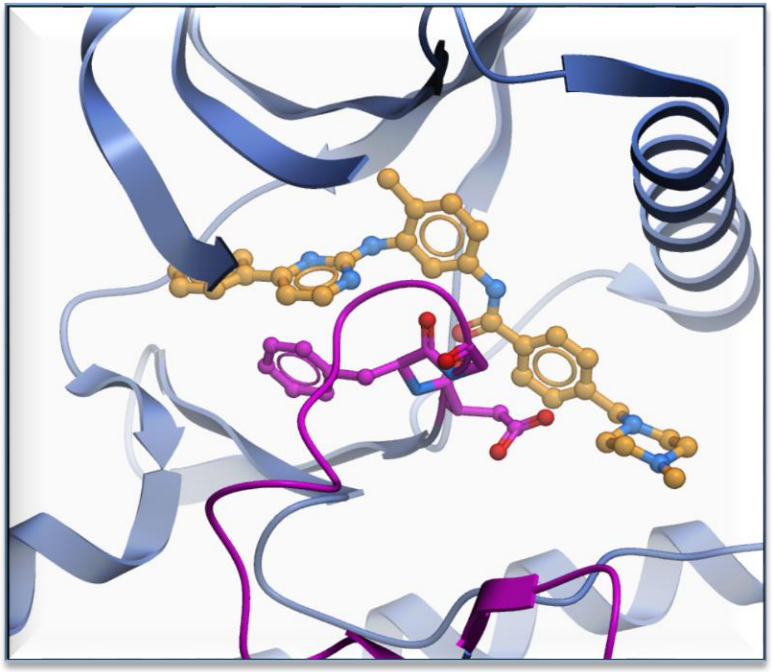
Imatinib and other current GIST drugs bind into the KIT battery pack space (competitive ATP inhibitors)

Concept 2: To date, all approved GIST kinase inhibitors bind to the inactive conformation

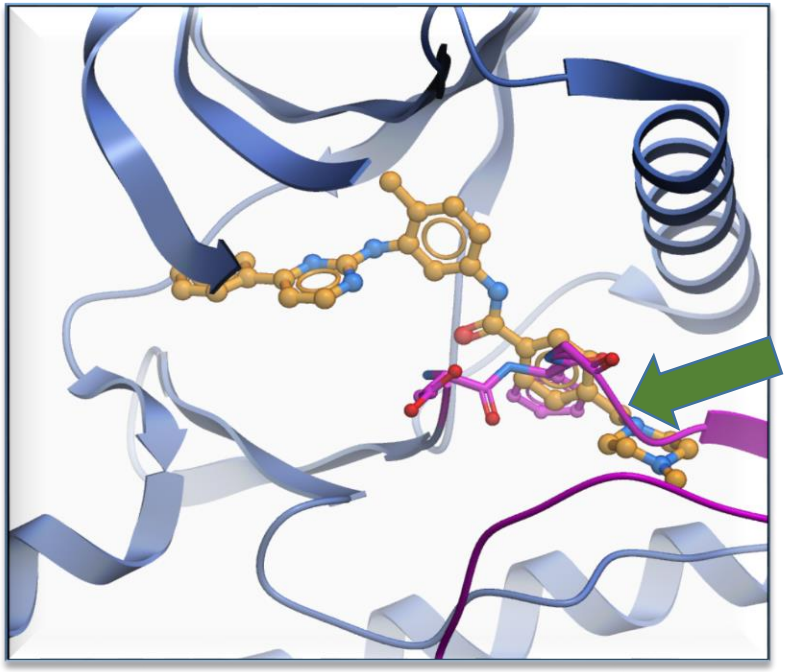


Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547

KIT activation loop mutations prevent Imatinib from binding to KIT/PDGFRα

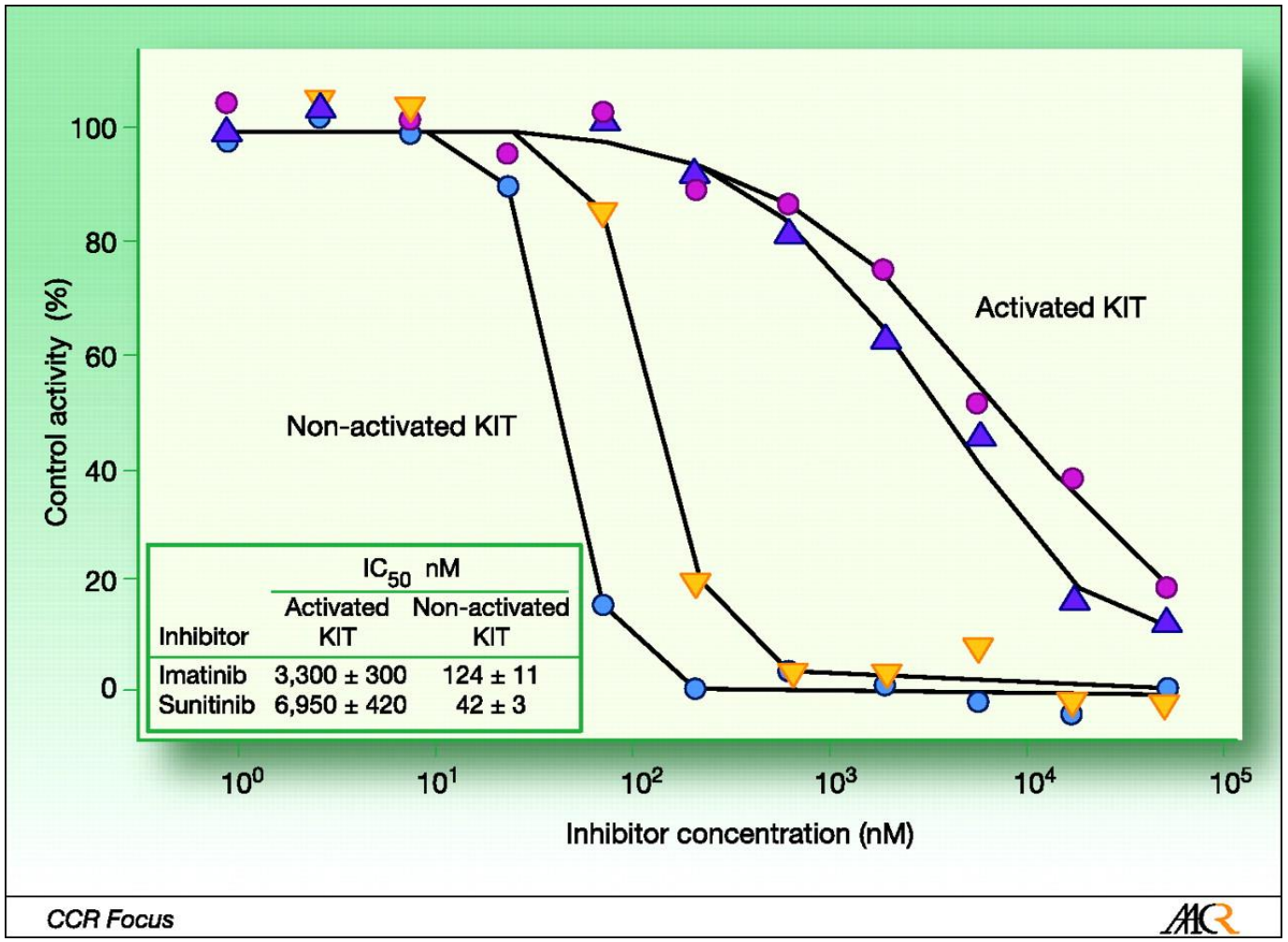


Inactive conformation
Activation loop closed confirmation
Type II inhibitors active



Active conformation
Activation loop open conformation
Type II inhibitors inactive

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

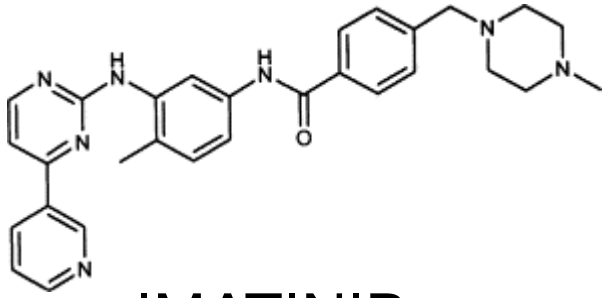


Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547

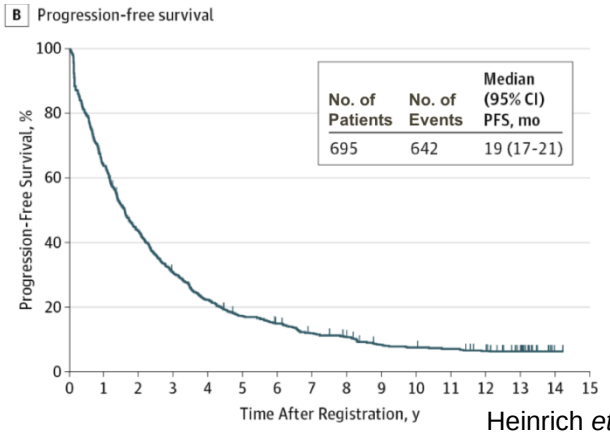
Concept 3

Drug-resistance is commonly due to the development of acquired mutations in the disease causing mutant kinase (e.g. KIT)

First line:

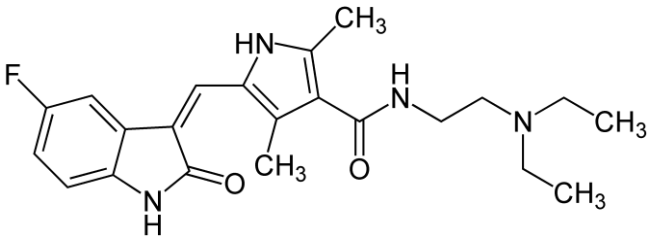


IMATINIB

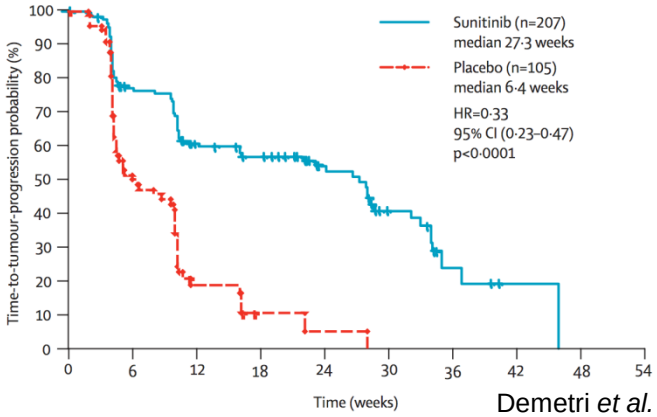


Heinrich *et al.* JAMA (2017)

Second line:

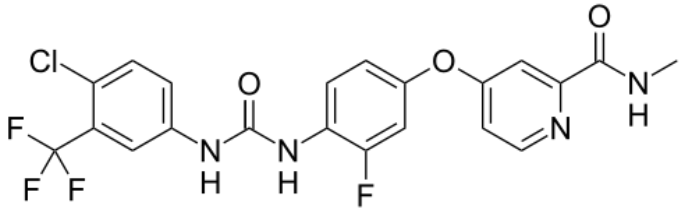


SUNITINIB

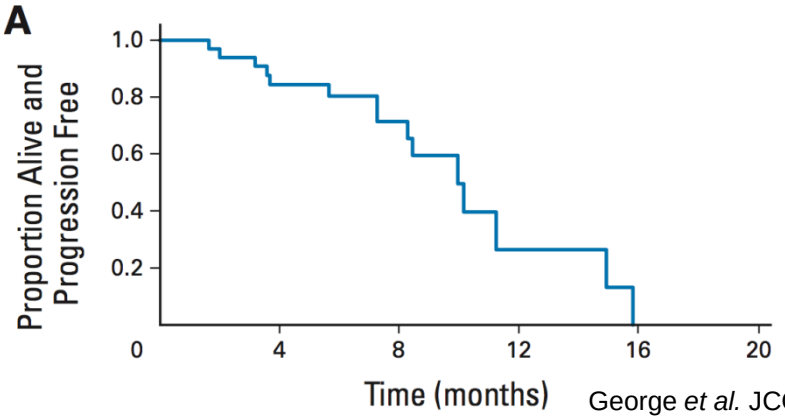


Demetri *et al.* Lancet (2006)

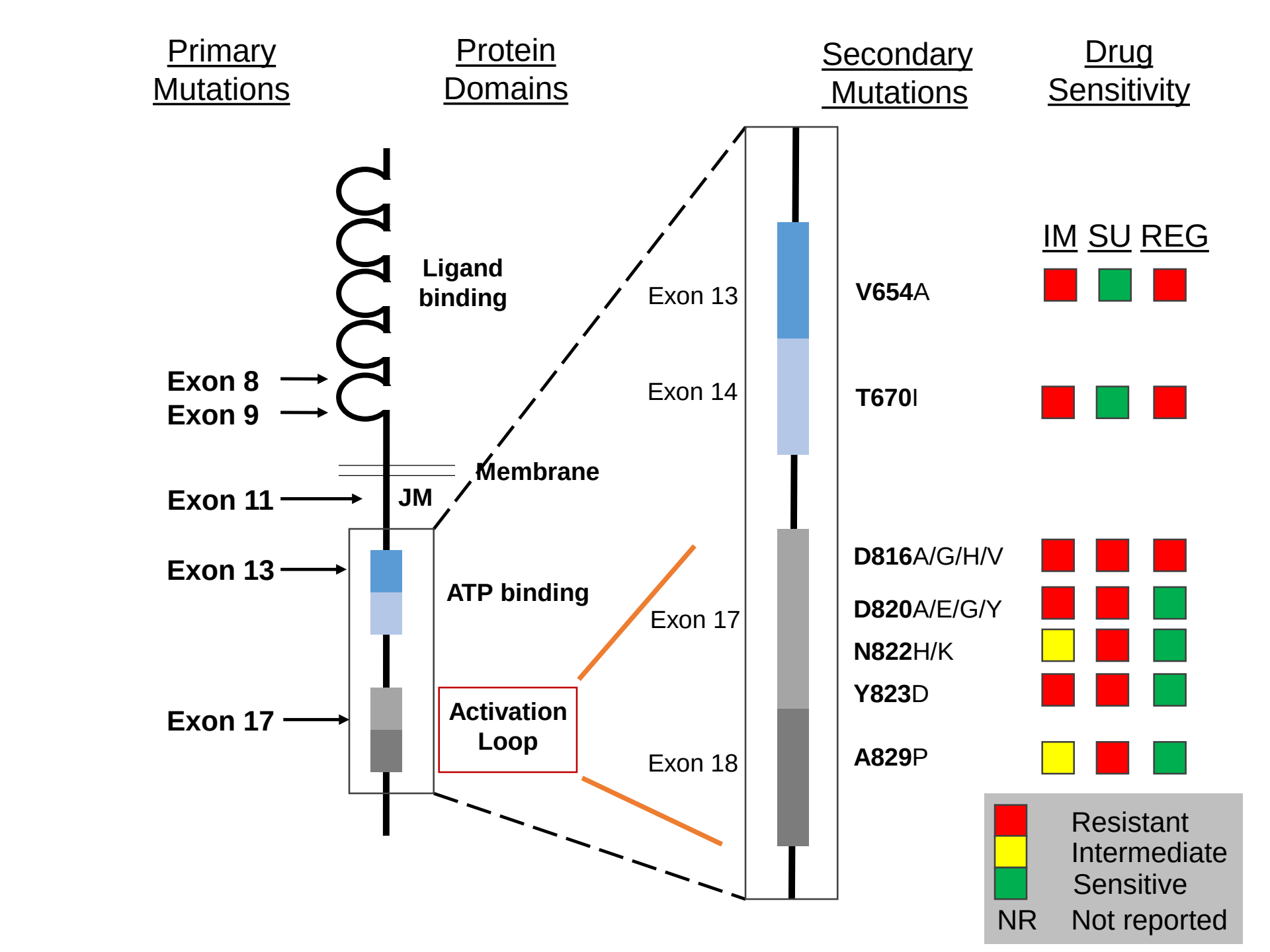
Third line:



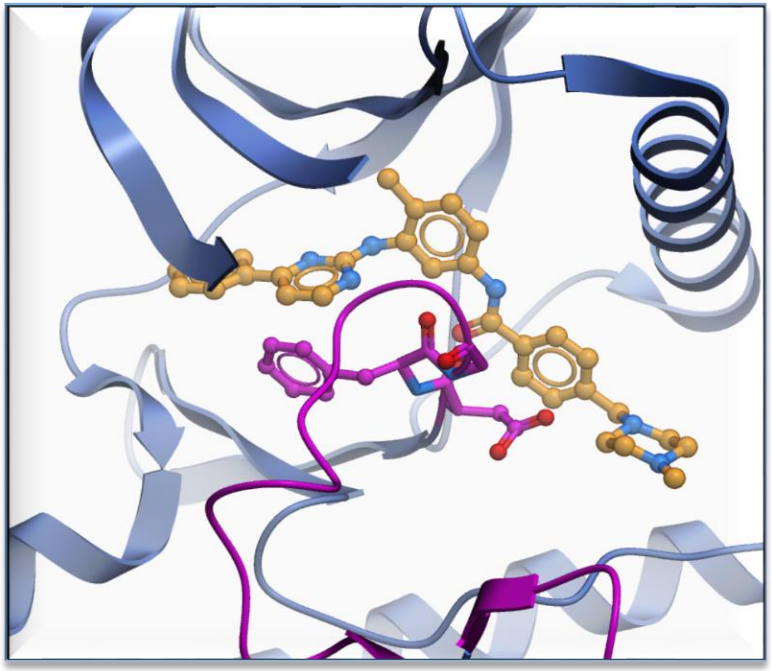
REGORAFENIB



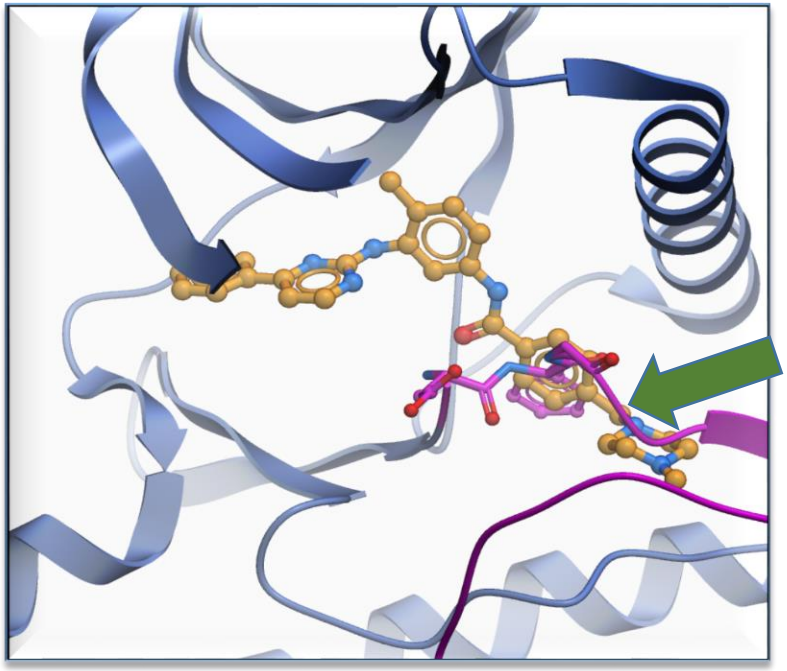
George *et al.* JCO (2012)


Primary Mutations
Protein Domains
Secondary Mutations
Drug Sensitivity
Ligand binding
Exon 8
Exon 9
Membrane
Exon 11
JM
Exon 13
ATP binding
Exon 17
Activation Loop
Exon 13
Exon 14
Exon 17
Exon 18
V654A
T670I
D816A/G/H/V
D820A/E/G/Y
N822H/K
Y823D
A829P
IM SU REG
Resistant
Intermediate
Sensitive
NR Not reported

Activation Loop Mutations Force KIT/PDGFRA into the Active Conformation



Inactive conformation
Activation loop closed confirmation
Type II inhibitors active



Active conformation
Activation loop open conformation
Type II inhibitors inactive