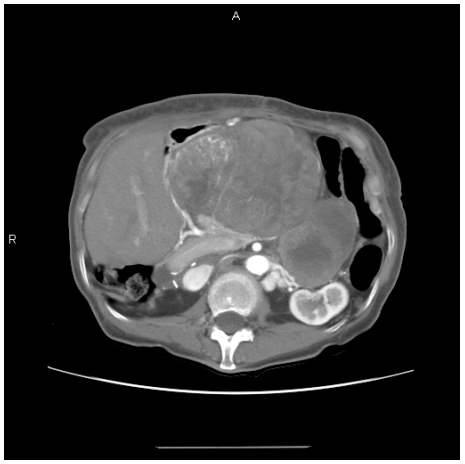
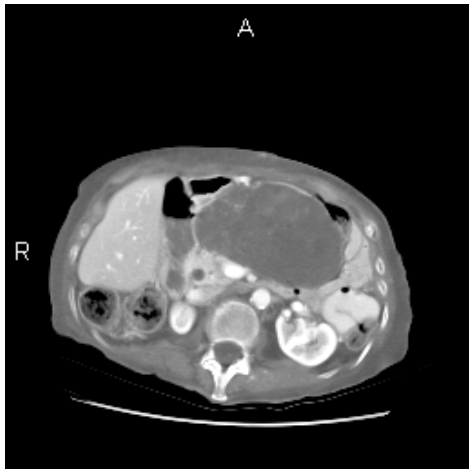
2008-2018

Ten Years of Advancements in GIST Research, Therapy & Survival





Dr. Michael Heinrich, M.D.

GSI Annual Summit Conference

September 2018

KNIGHT CANCER INSTITUTE
Oregon Health & Science University
OHSU

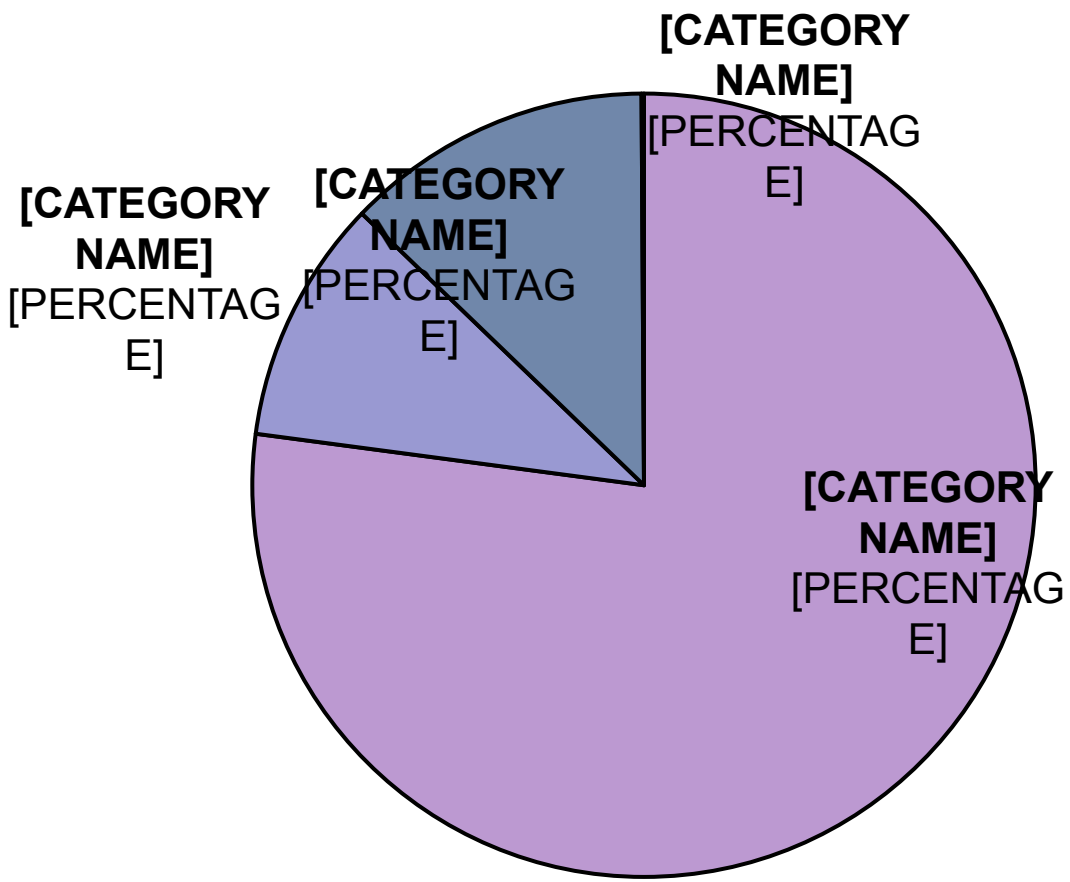
Overview

- Advances in GIST biology/pathology
- Update on front-line imatinib
- Adjuvant therapy and mutation status
- Current treatment approaches for imatinib-resistant GIST
- The next generation of GIST treatments

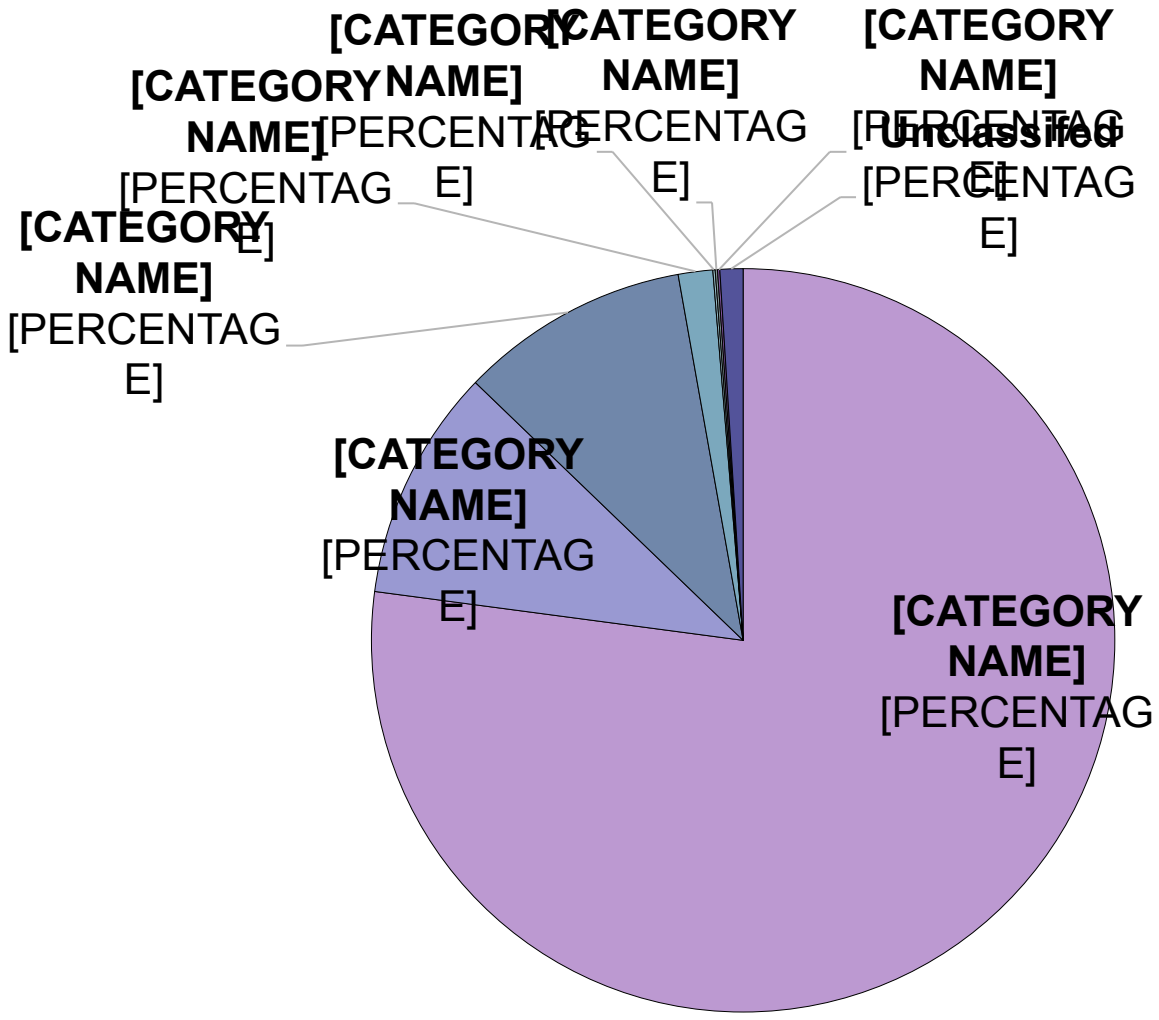
Not all GISTs are the Same

- GIST represent a collection of cancers linked by a common histology and presumed shared cell of origin (ICC)
- Most GIST are driven by a mutant kinase
- The type of underlying mutation(s) in a given patient's GIST significantly impacts treatment response and potential mechanisms of acquired resistance

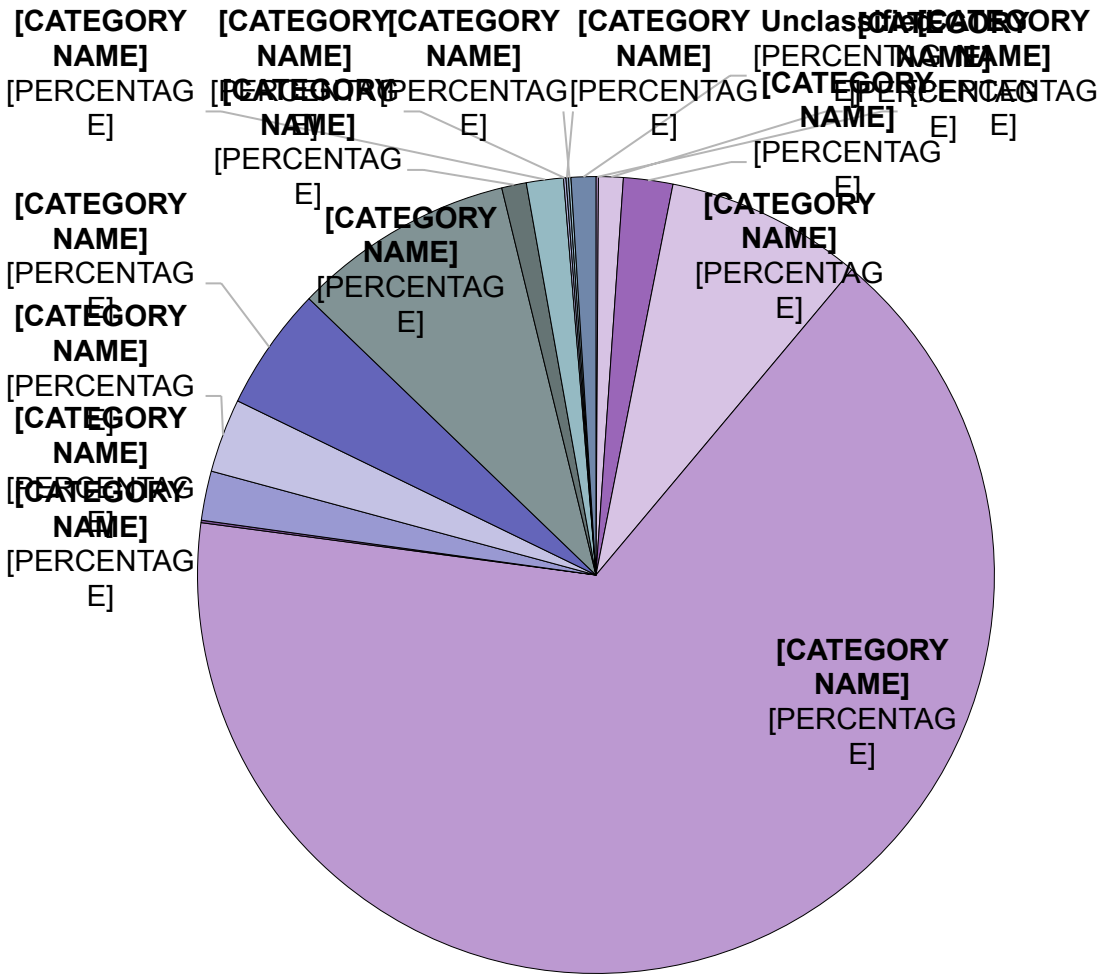
Molecular Classification of GIST 2008



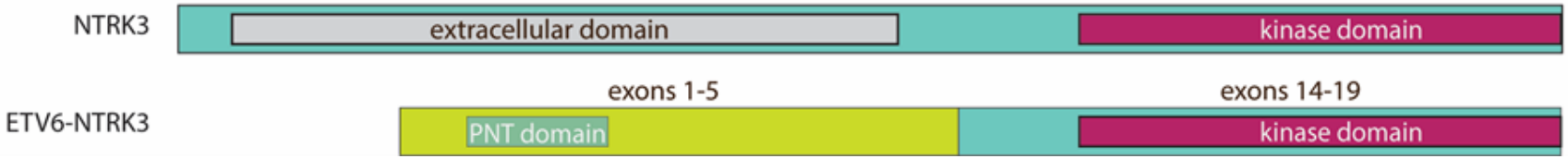
Molecular Classification of GIST 2018

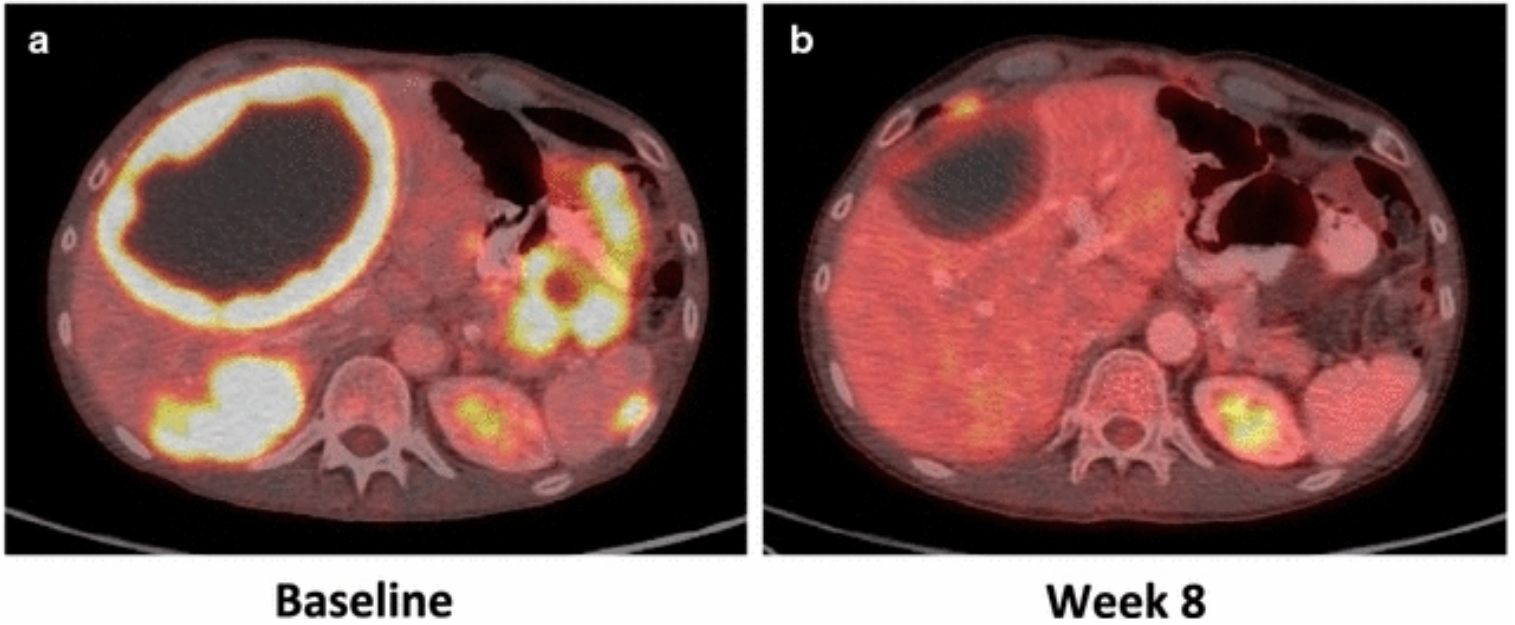


Molecular Classification of GIST 2018
“No subgroup left behind”



Precision Therapy of NTRK3-Translocated GIST

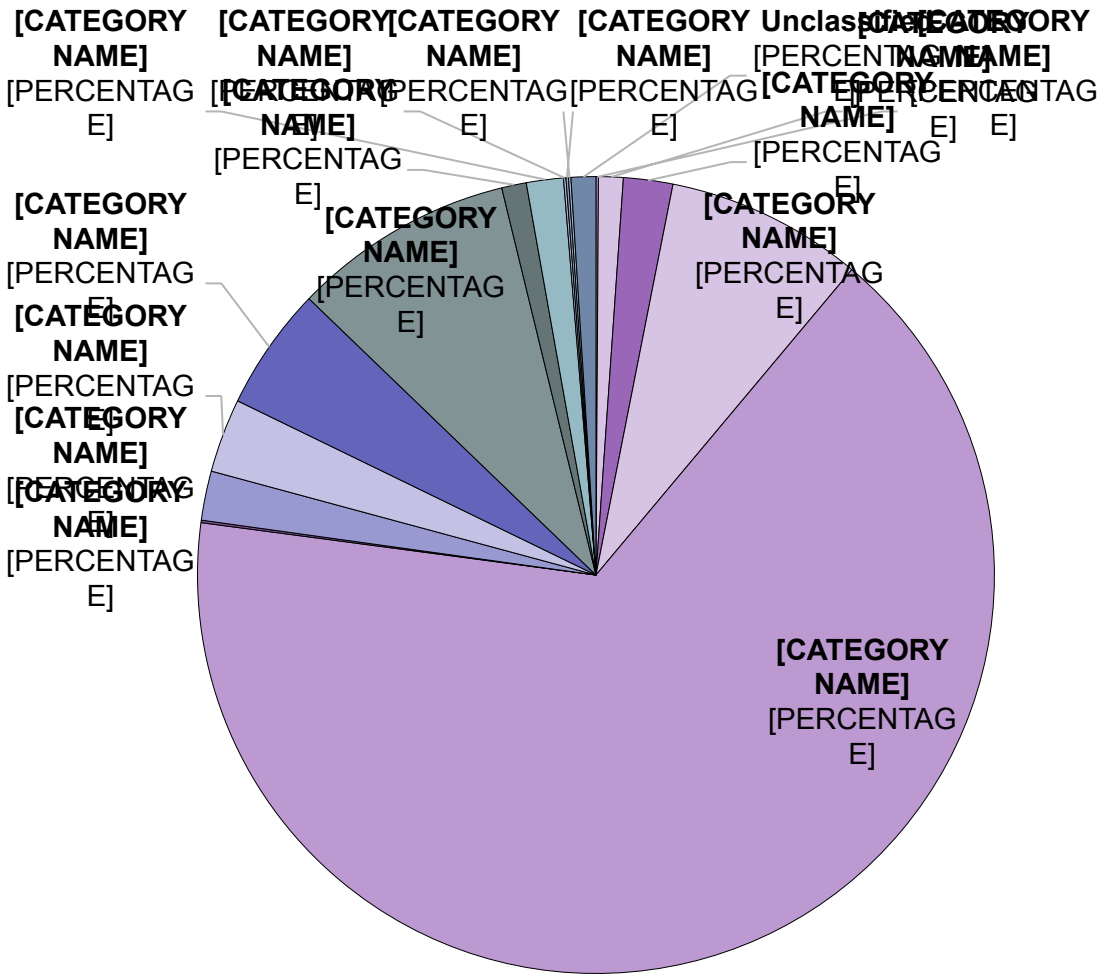




Shi et al., Journal of Translational Medicine, 2016

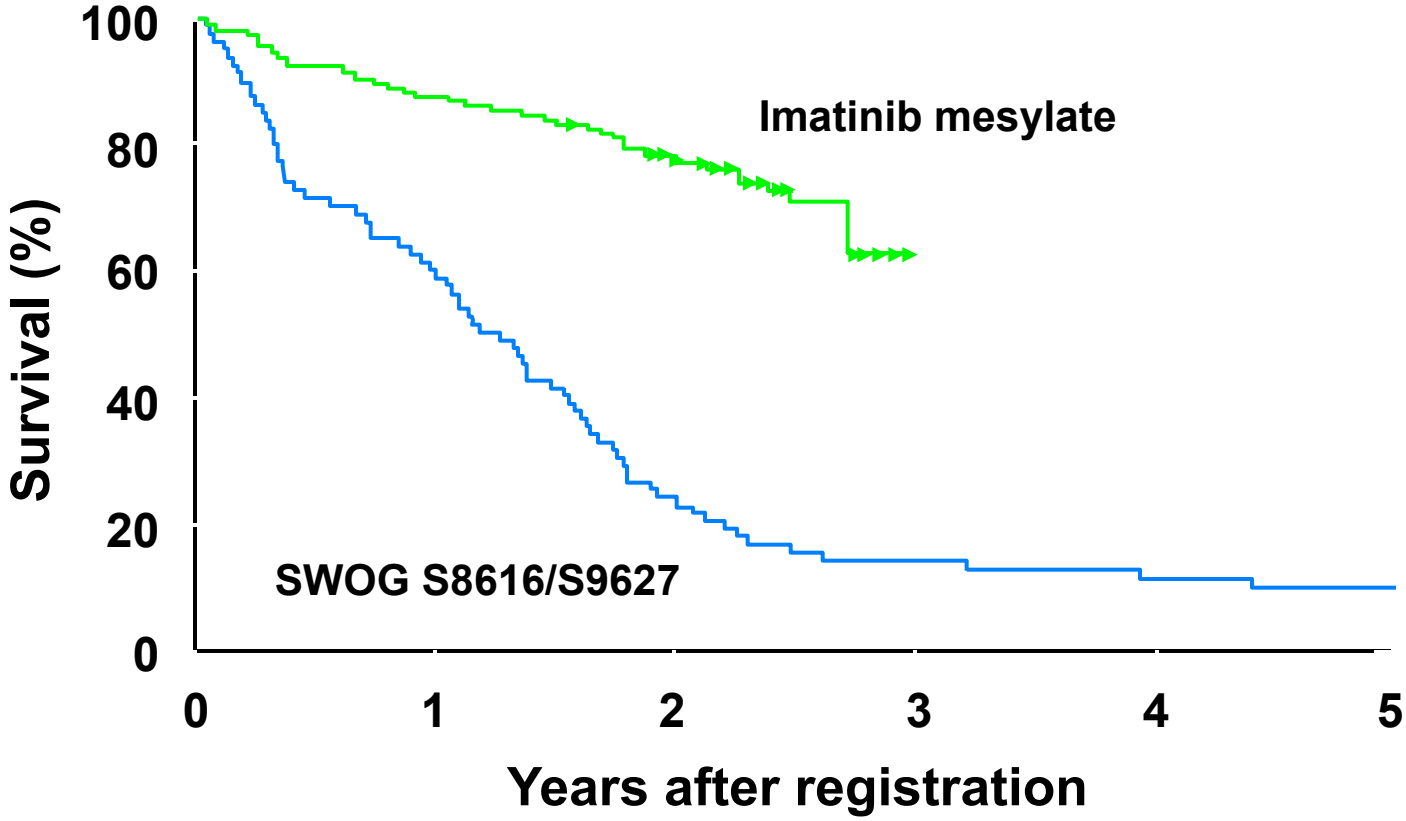
Real Estate: “location, location, location”

GIST: “mutation, mutation, mutation”



Front-line Therapy of Advanced Disease

Imatinib Mesylate in GIST: Pivotal Phase 2 Study—Overall Survival

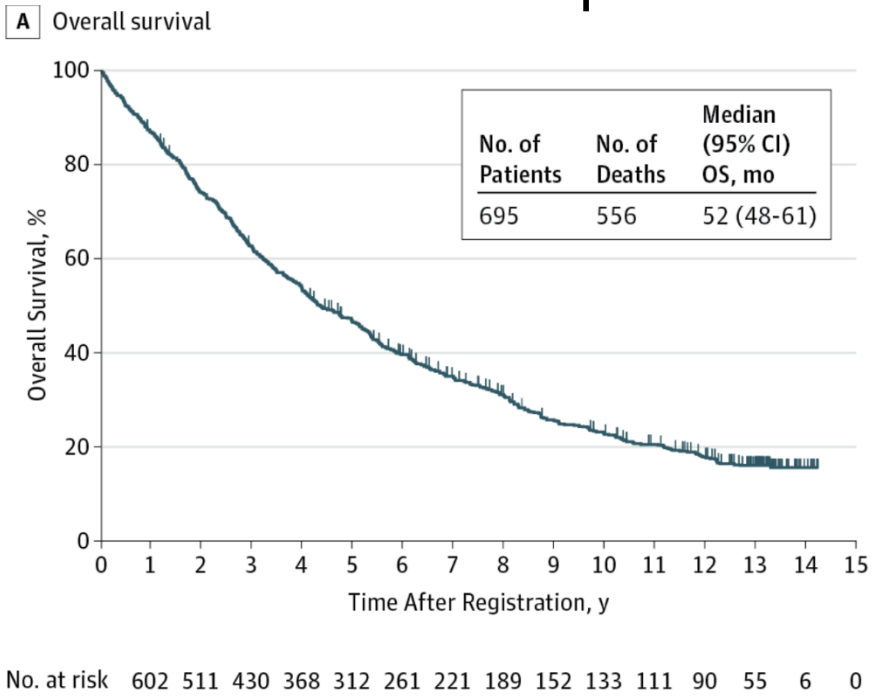


- With a median follow-up of 34 months, median survival has not been reached

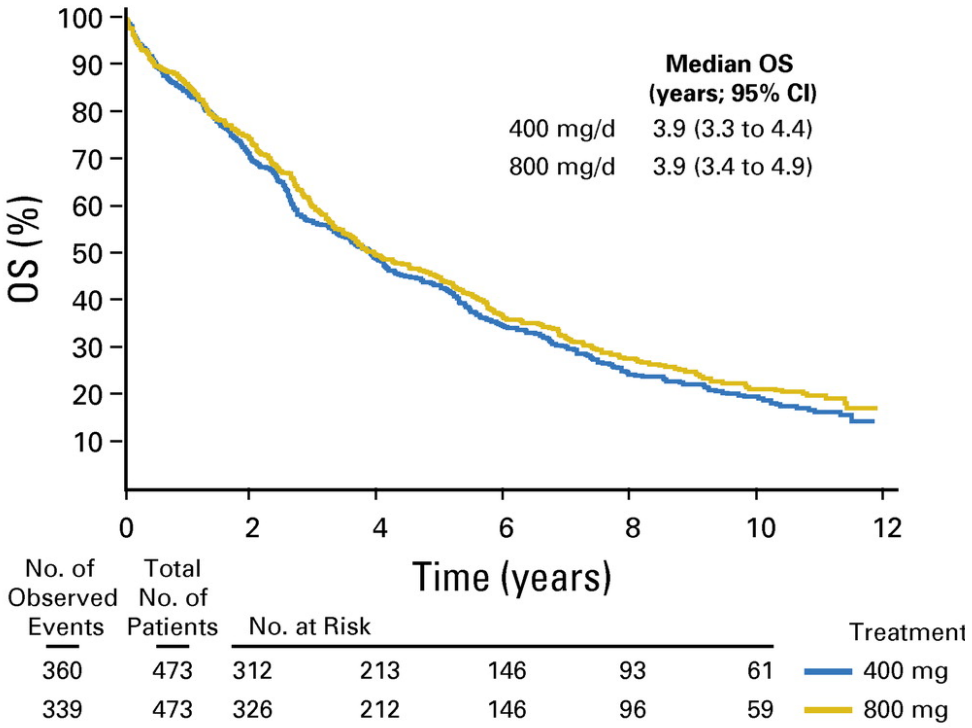
Blanke et al. ASCO 2004 Gastrointestinal Cancers Symposium. Abstract 2.

Phase 3 Front-line Imatinib for Treatment of Advanced/Metastatic GIST

S0033 695 patients



EORTC 946 patients



A: Heinrich et al. JAMA Oncology 2017
B: Casali, et. al, Journal of Clinical Oncology 2017

Phase 3 Studies of Front-line Imatinib for Advanced GIST

S0033 (US-Canada)

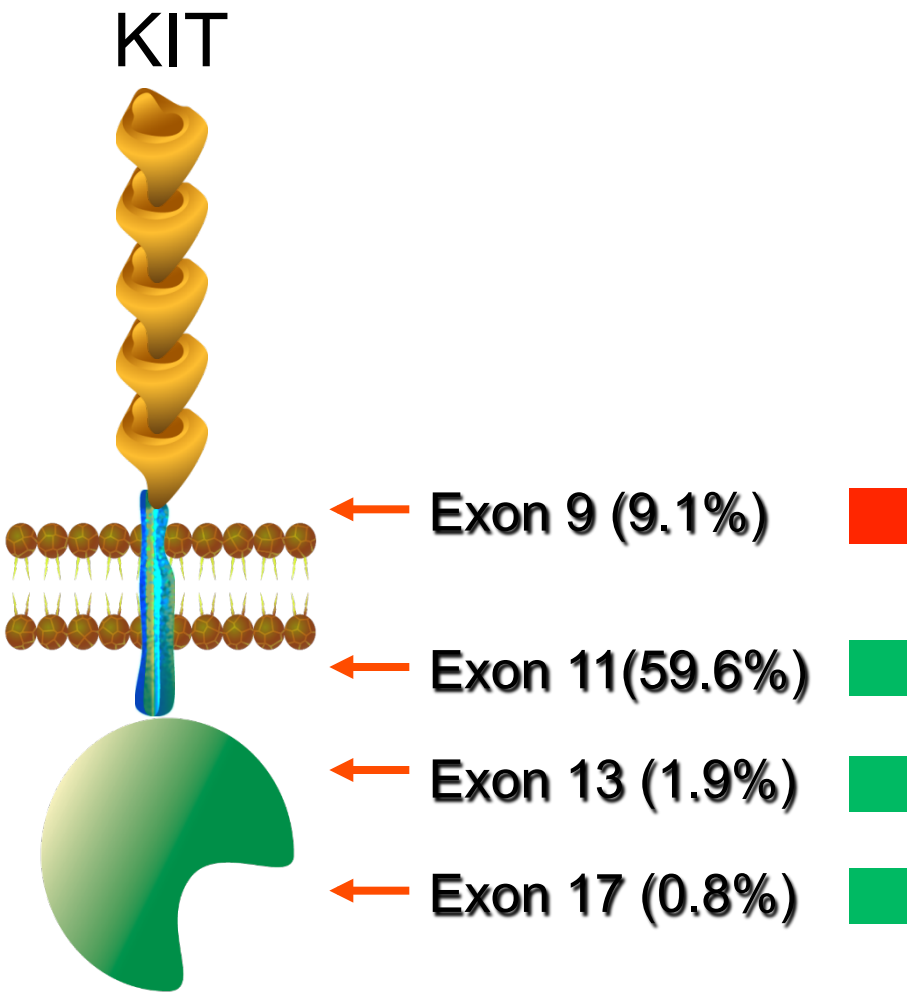
- 10 year estimate of overall survival: 23%
- 10 year estimate of PFS: 7%

EORTC, Italy, Australia

- 10 year estimate of overall survival: ~20%
- 10 year estimate of PFS: ~9%

S0033: Heinrich et al. JAMA Oncology 2017
EORTC: Casali, et. al, Journal of Clinical Oncology 2017

Dosing Recommendations for KIT-mutant GIST from Phase 3 Studies

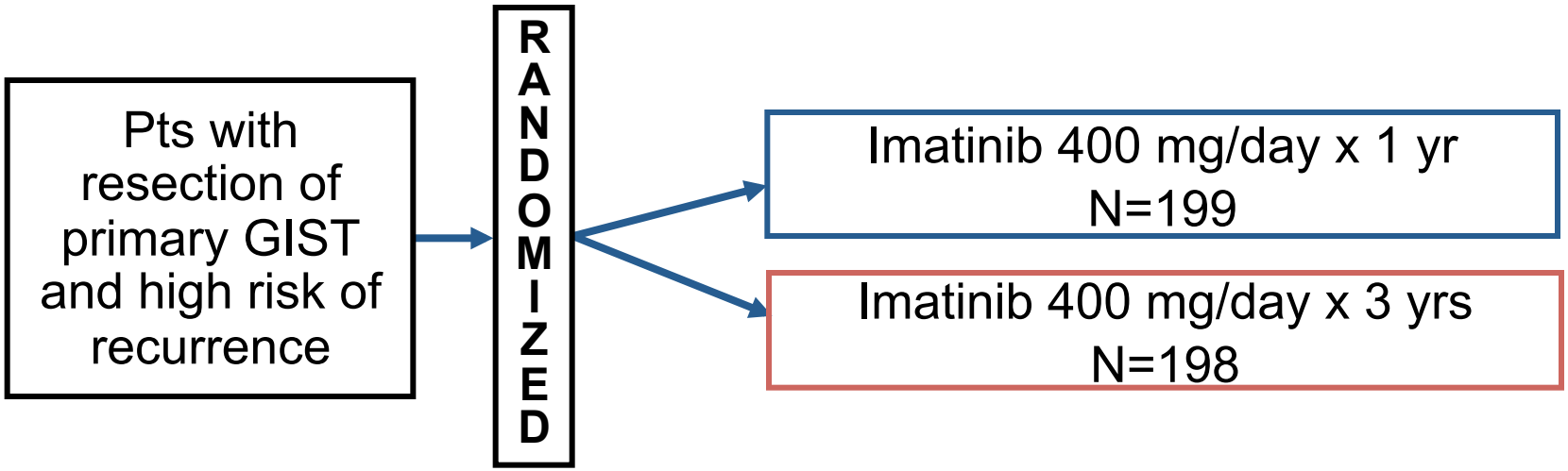


Imatinib 400 mg

Imatinib 800 mg

Adjuvant Therapy

1 Yr vs 3 Yrs of Adjuvant Imatinib: SSGXVIII

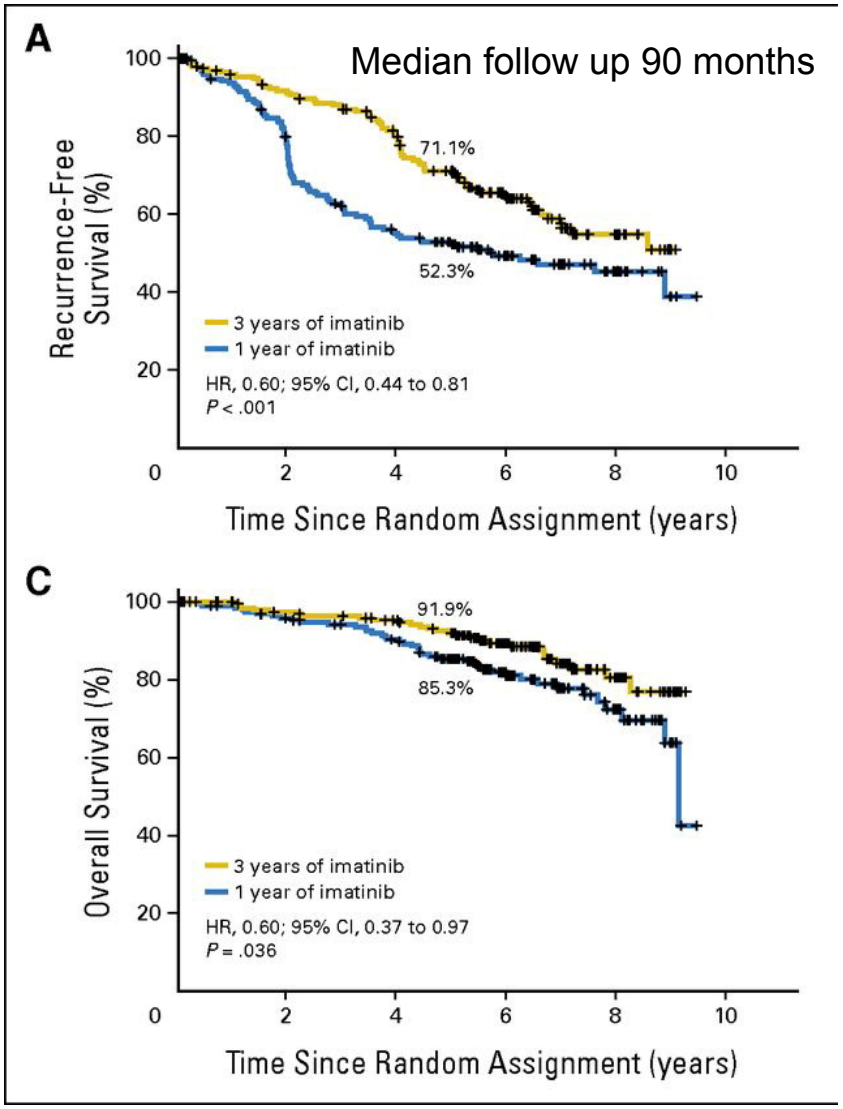


- Primary endpoint
  - RFS
- Secondary endpoints
  - AEs and OS

– High risk of recurrence: the “rule of 10”

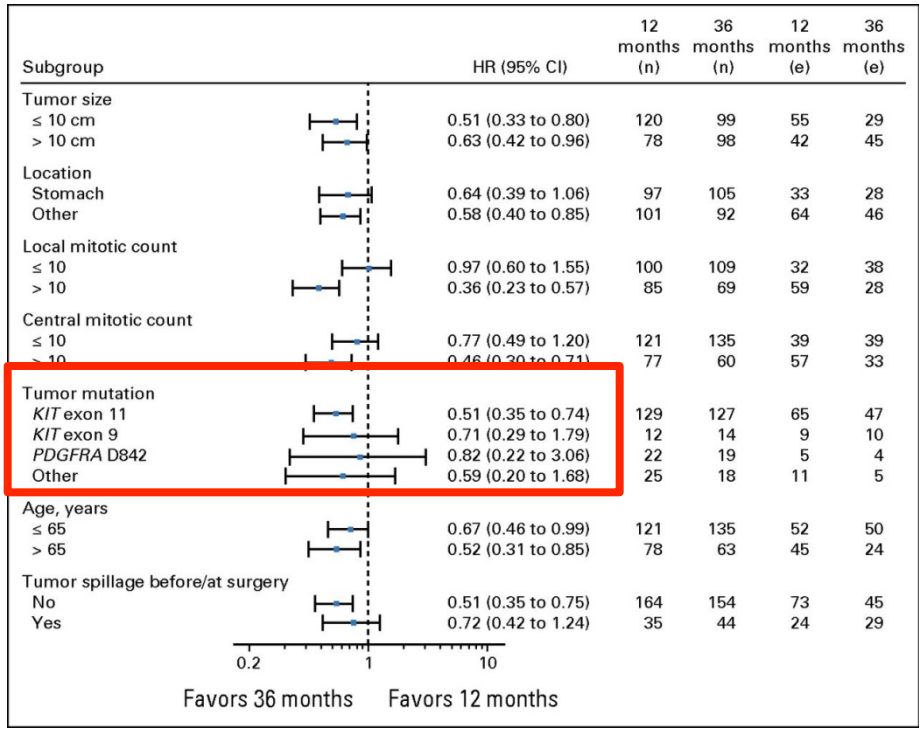
Joensuu. *ASCO.* 2011 (abstr LBA 1).

SSGXVIII: Intention to Treat Analysis



Joensuu et al., JCO 2016

Genotyping and Patient Selection for Adjuvant Imatinib Therapy



Subgroup	HR (95% CI)	12 months (n)	36 months (n)	12 months (e)	36 months (e)
Tumor size					
≤ 10 cm	0.51 (0.33 to 0.80)	120	99	55	29
> 10 cm	0.63 (0.42 to 0.96)	78	98	42	45
Location					
Stomach	0.64 (0.39 to 1.06)	97	105	33	28
Other	0.58 (0.40 to 0.85)	101	92	64	46
Local mitotic count					
≤ 10	0.97 (0.60 to 1.55)	100	109	32	38
> 10	0.36 (0.23 to 0.57)	85	69	59	28
Central mitotic count					
≤ 10	0.77 (0.49 to 1.20)	121	135	39	39
> 10	0.46 (0.30 to 0.71)	77	60	57	33
Tumor mutation					
KIT exon 11	0.51 (0.35 to 0.74)	129	127	65	47
KIT exon 9	0.71 (0.29 to 1.79)	12	14	9	10
PDGFRA D842	0.82 (0.22 to 3.06)	22	19	5	4
Other	0.59 (0.20 to 1.68)	25	18	11	5
Age, years					
≤ 65	0.67 (0.46 to 0.99)	121	135	52	50
> 65	0.52 (0.31 to 0.85)	78	63	45	24
Tumor spillage before/at surgery					
No	0.51 (0.35 to 0.75)	164	154	73	45
Yes	0.72 (0.42 to 1.24)	35	44	24	29

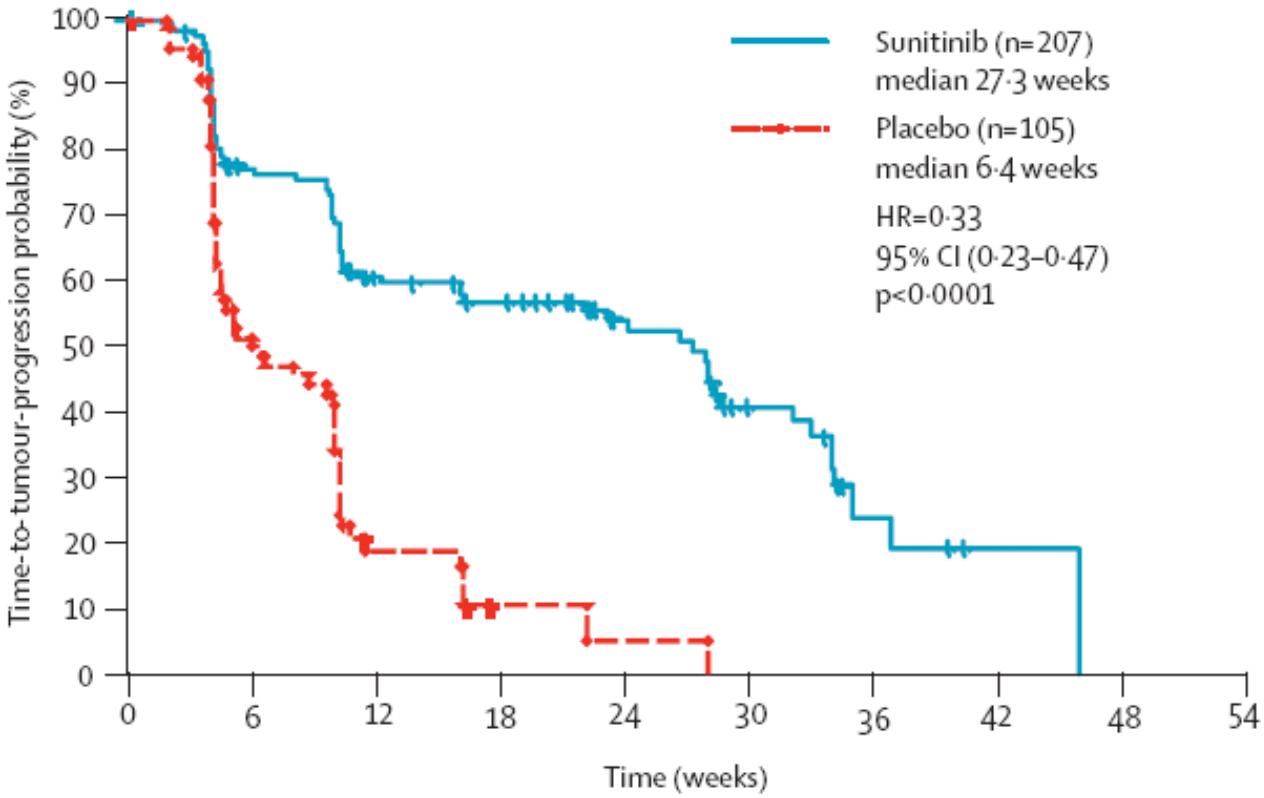
Recommendations

- Treat patients with *KIT* exon11-mutant GIST
- Consider high-dose imatinib for patients with KIT exon 9-mutant GIST
- No adjuvant therapy for patients with *KIT/PDGFRA* WT GIST
- No adjuvant therapy for patients with *PDGFRA* D842V-mutant GIST

Joensuu et al., JCO 2016

Management of Imatinib-resistant Disease

Sunitinib in Patients With Imatinib-Refractory GIST: Time to Tumor Progression

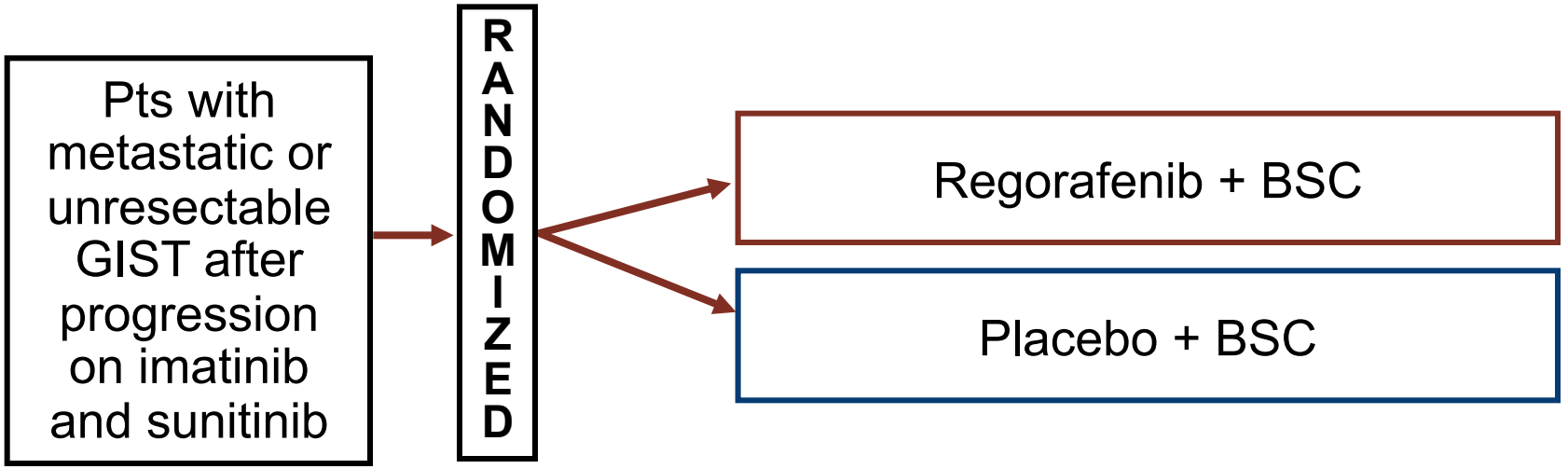


Number at risk

Sunitinib	207	106	67	53	34	18	5	1	0
Placebo	105	36	9	2	1	0	0	0	0

Reproduced with permission from Demetri. *Lancet*. 2006;368:1329.

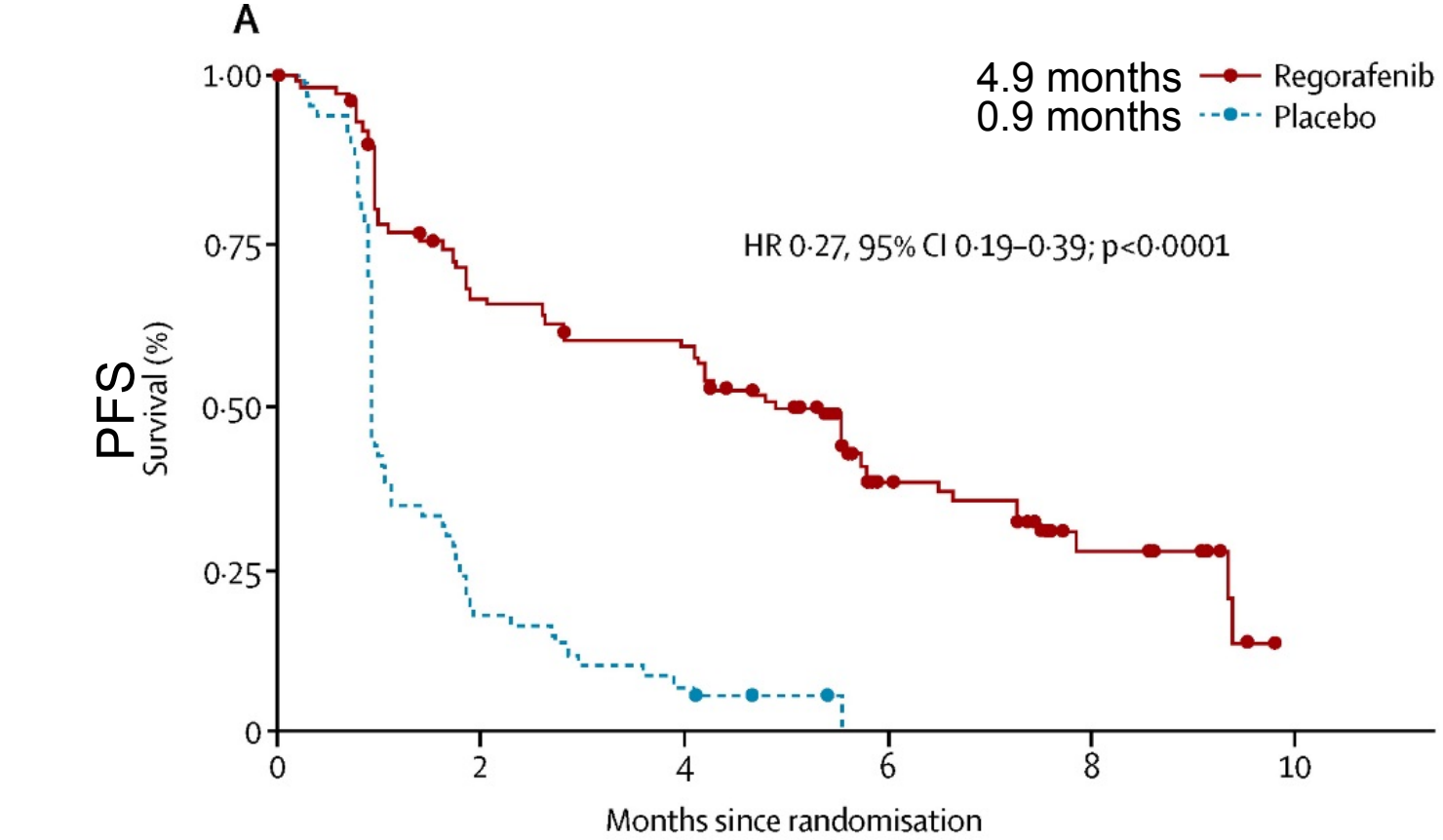
Phase III Trial of Regorafenib in Advanced GIST



- Primary endpoint: PFS
- Secondary endpoints: OS, TTP, RR, and DOR

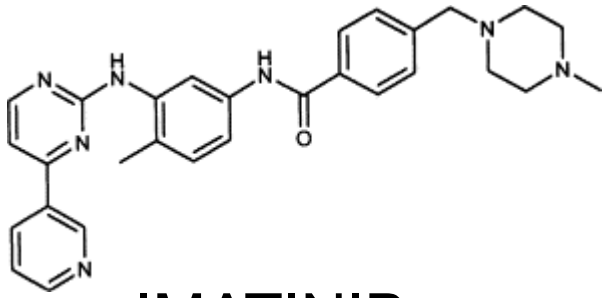
US National Institutes of Health website. http://www.clinicaltrials.gov/ct2/show/study/NCT01271712. Accessed 08/02/11.

Phase III Trial of Regorafenib in Advanced GIST

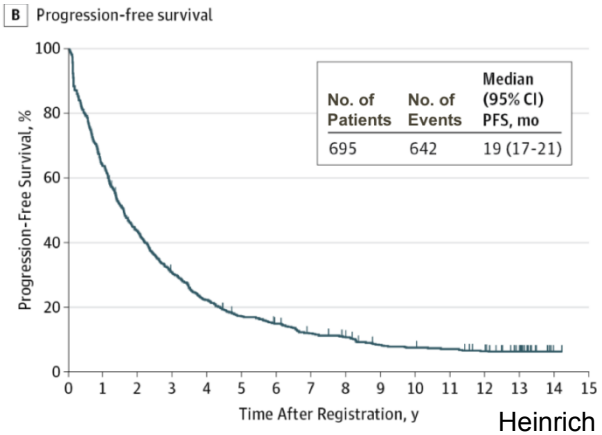


Demetri et al., The Lancet 2013 381, 295-302DOI: (10.1016/S0140-6736(12)61857-1)

First line:

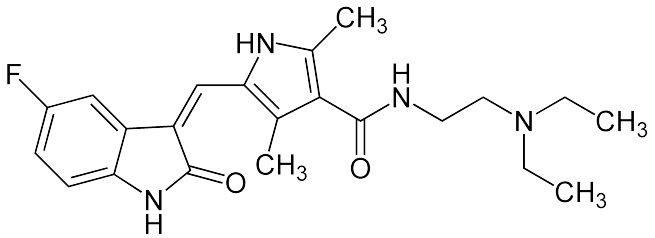


IMATINIB

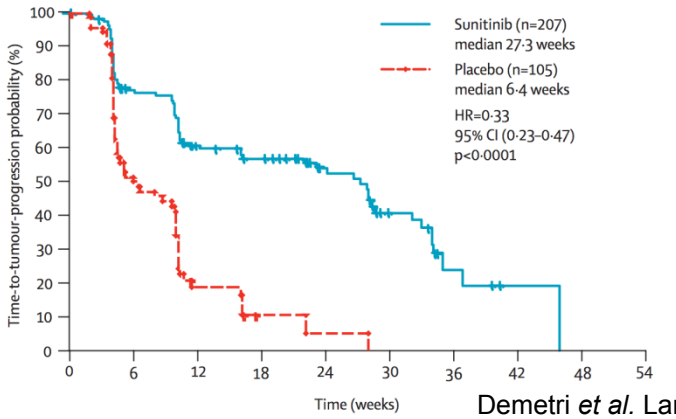


Heinrich *et al.* JAMA (2017)

Second line:

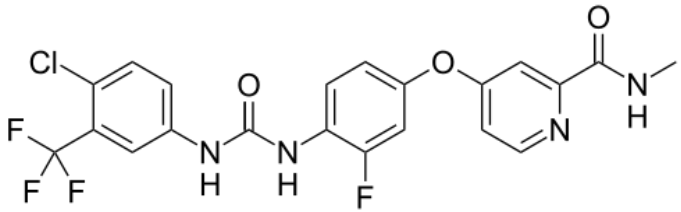


SUNITINIB

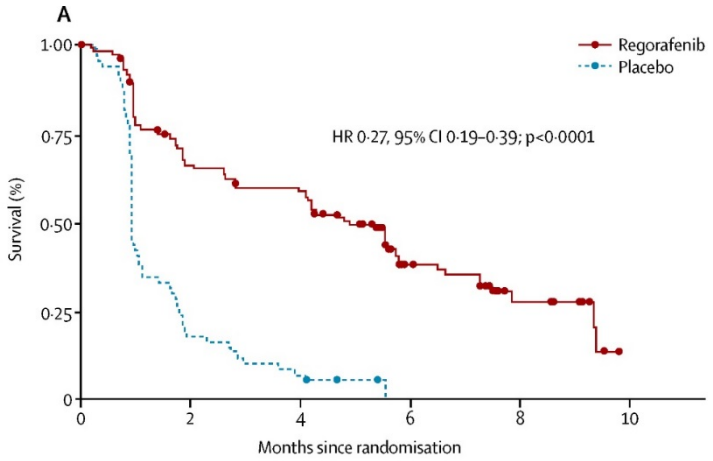


Demetri *et al.* Lancet (2006)

Third line:



REGORAFENIB



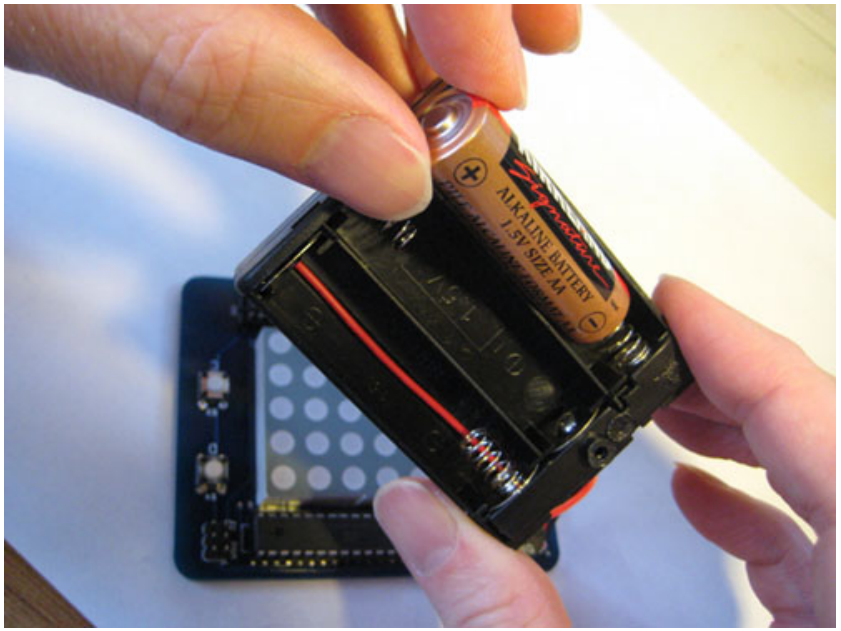
Demetri *et al.* Lancet (2013)

Treatment of Imatinib-resistant GIST: The Next Generation

Background

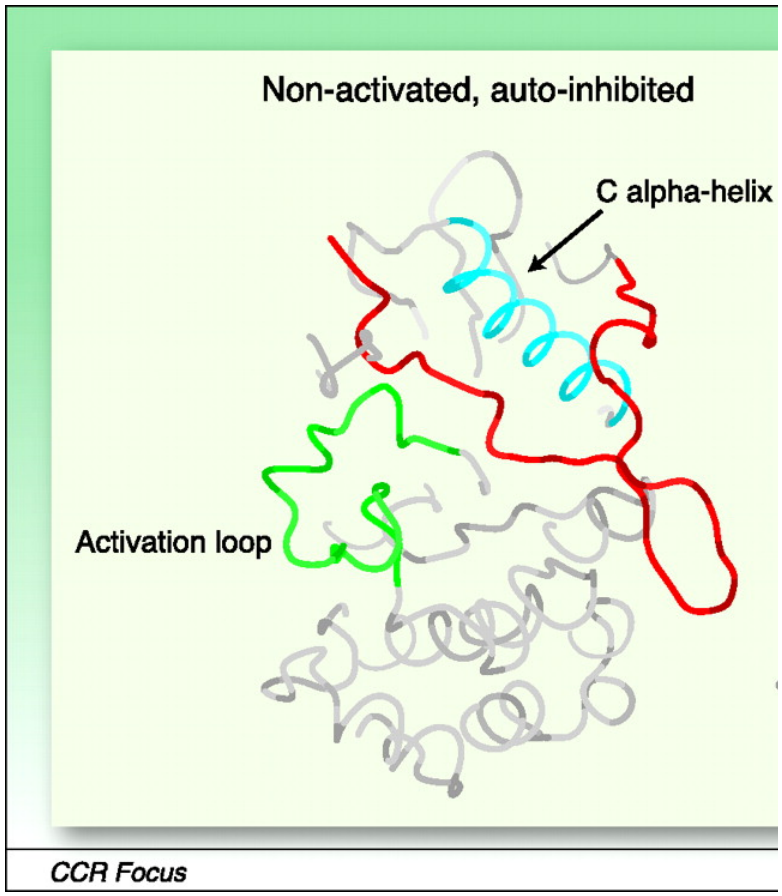
- Inhibitors of KIT/PDGFRA (TKIs) such as imatinib and sunitinib have transformed the medical treatment of advanced GIST
- However, disease control in the metastatic setting is limited by the development of drug-resistant clones
- Concept 1: To date, all approved TKIs used for the treatment of GIST are 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)

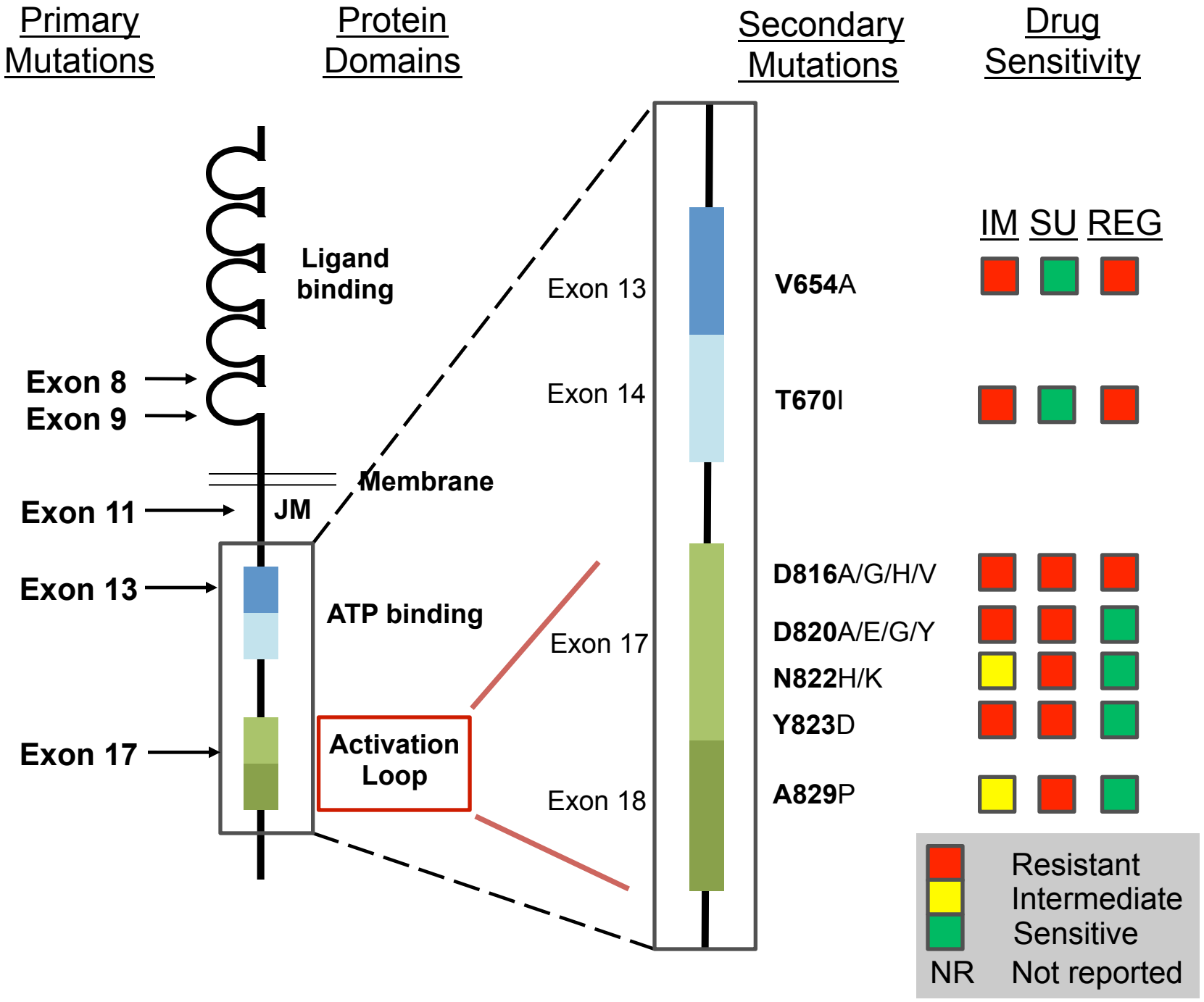
Concept 2: To date, all approved GIST kinase inhibitors bind to the inactive conformation



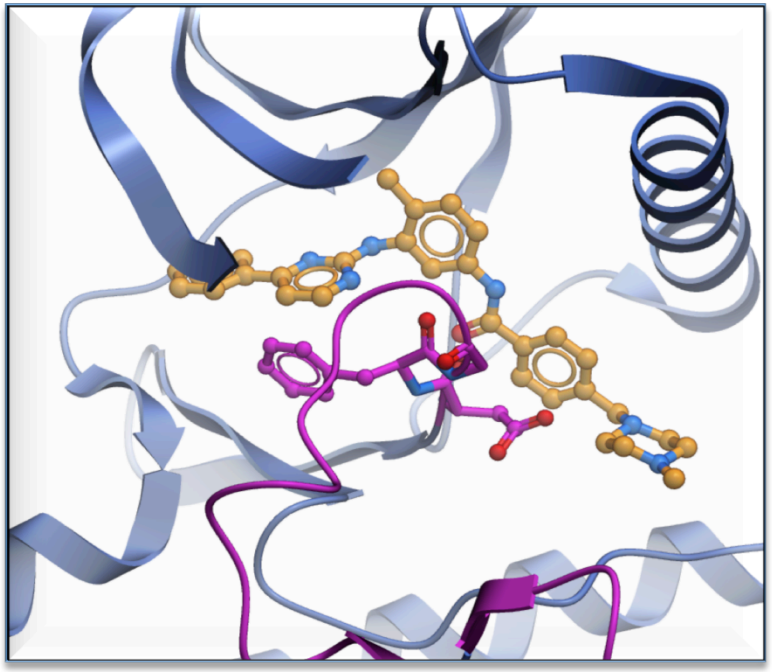
Adapted from Gajiwala K. S. et.al. PNAS 2009;106:1542-1547

Concept 3

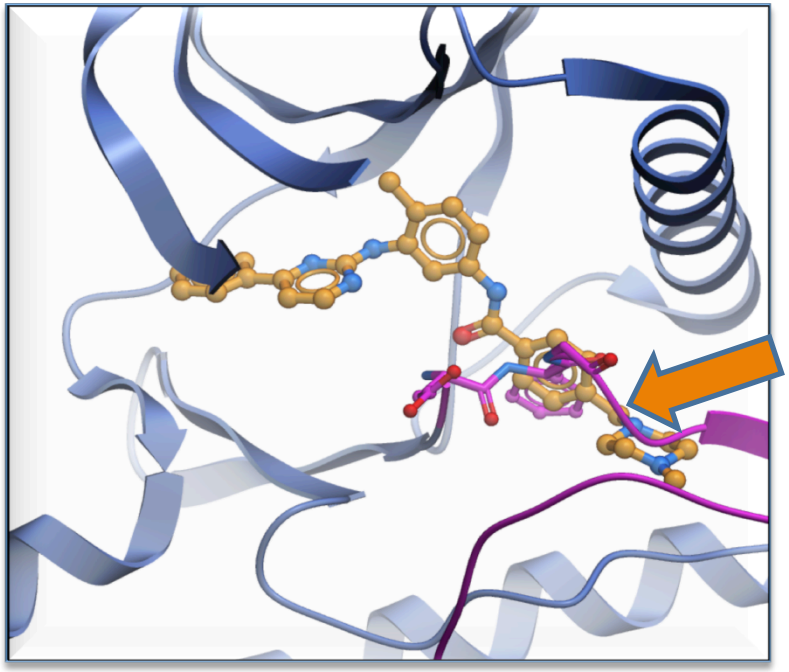
Drug-resistance is commonly due to the development of acquired mutations in the disease-causing mutant-kinase (e.g. KIT)


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

Clinical activity of Avapritinib (BLU-285) in advanced GIST

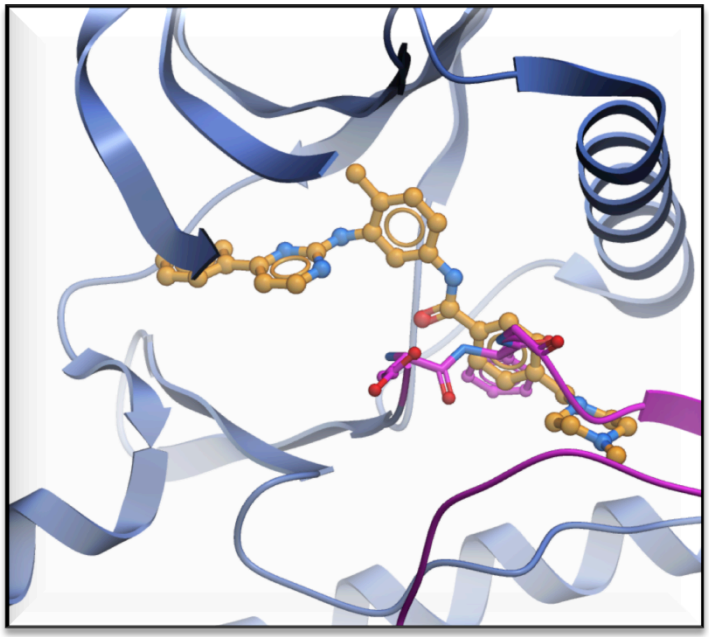
Michael Heinrich[1], Robin Jones[2], Margaret von Mehren[3], Patrick Schoffski[4], Sebastian Bauer[5], Olivier Mir[6], Philippe Cassier[7], Ferry Eskens[8], Hongliang Shi[9], Terri Alvarez-Diez[9], Oleg Schmidt-Kittler[9], Mary Ellen Healy[9], Beni Wolf[9], Suzanne George[10]

[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

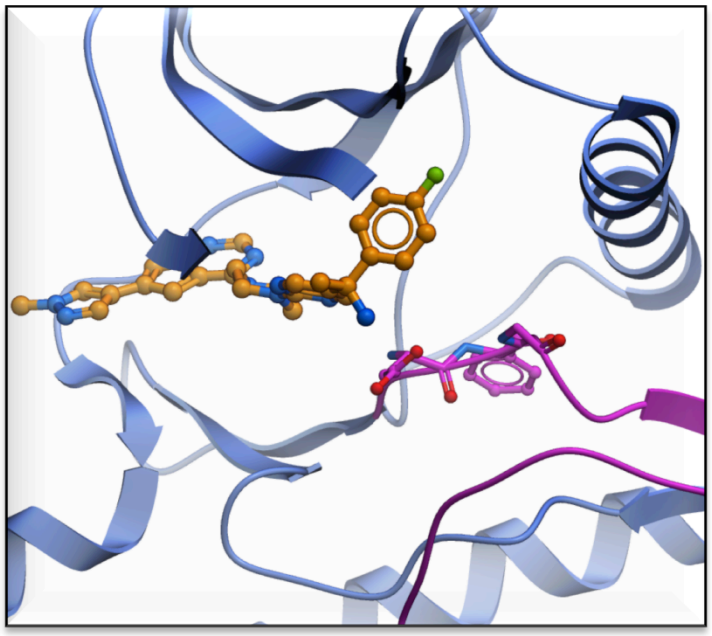
CTOS 2017

Presented by: Dr. Michael Heinrich

Avapritinib is a potent type 1 KIT/PDGFRα inhibitor that binds to the active conformation of the kinase

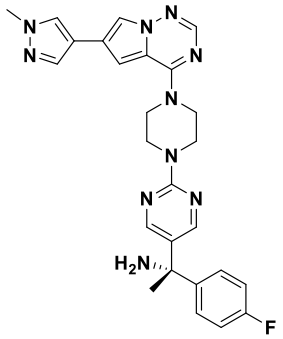


Imatinib
Activation loop open

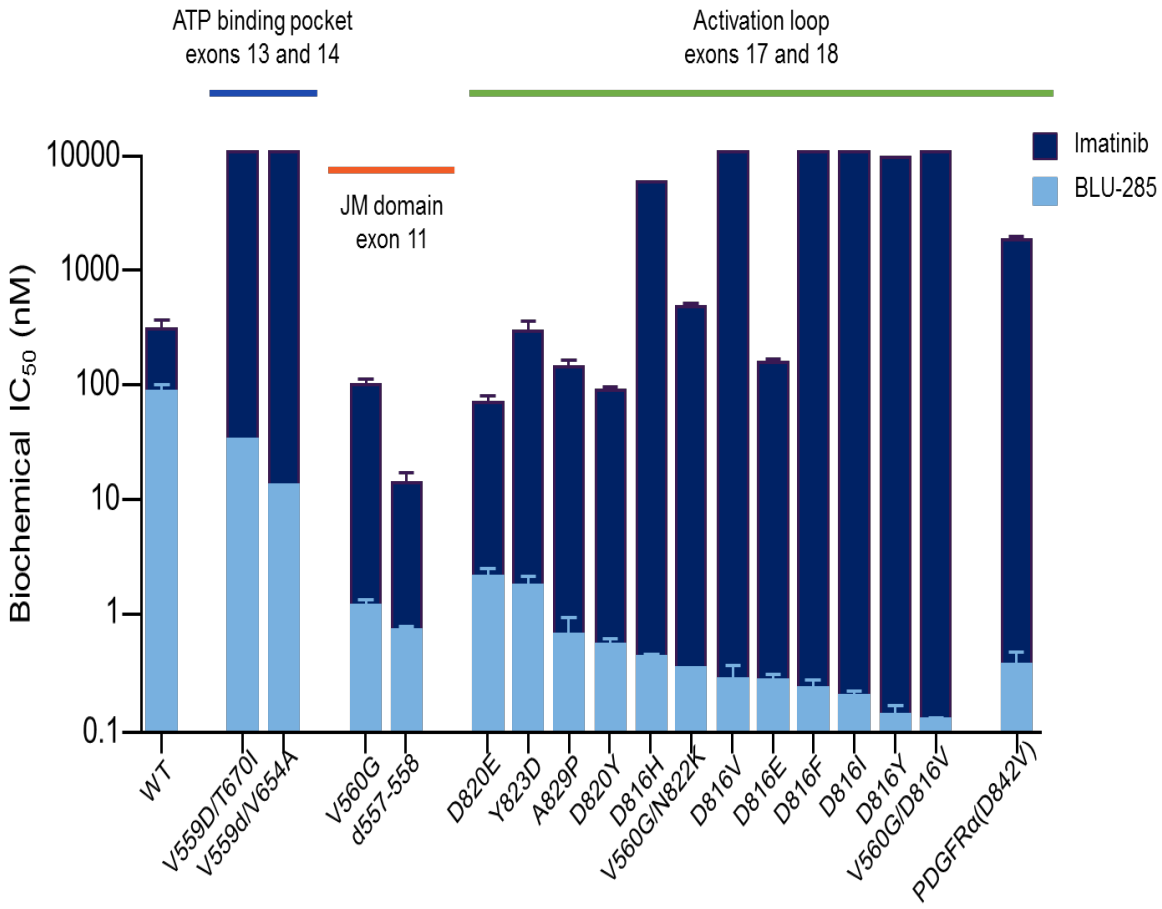


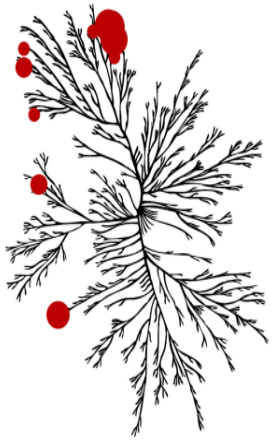
Avapritinib
Activation loop open

Avapritinib

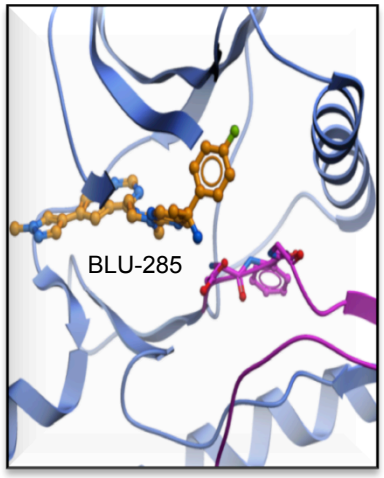


Avapritinib: highly potent and selective targeting of KIT/ PDGFRα mutants





- High kinome selectivity*



- Binds active conformation

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

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*

Advanced GIST → MTD

- 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*

PDGFRα D842V-mutant GIST (n=50)

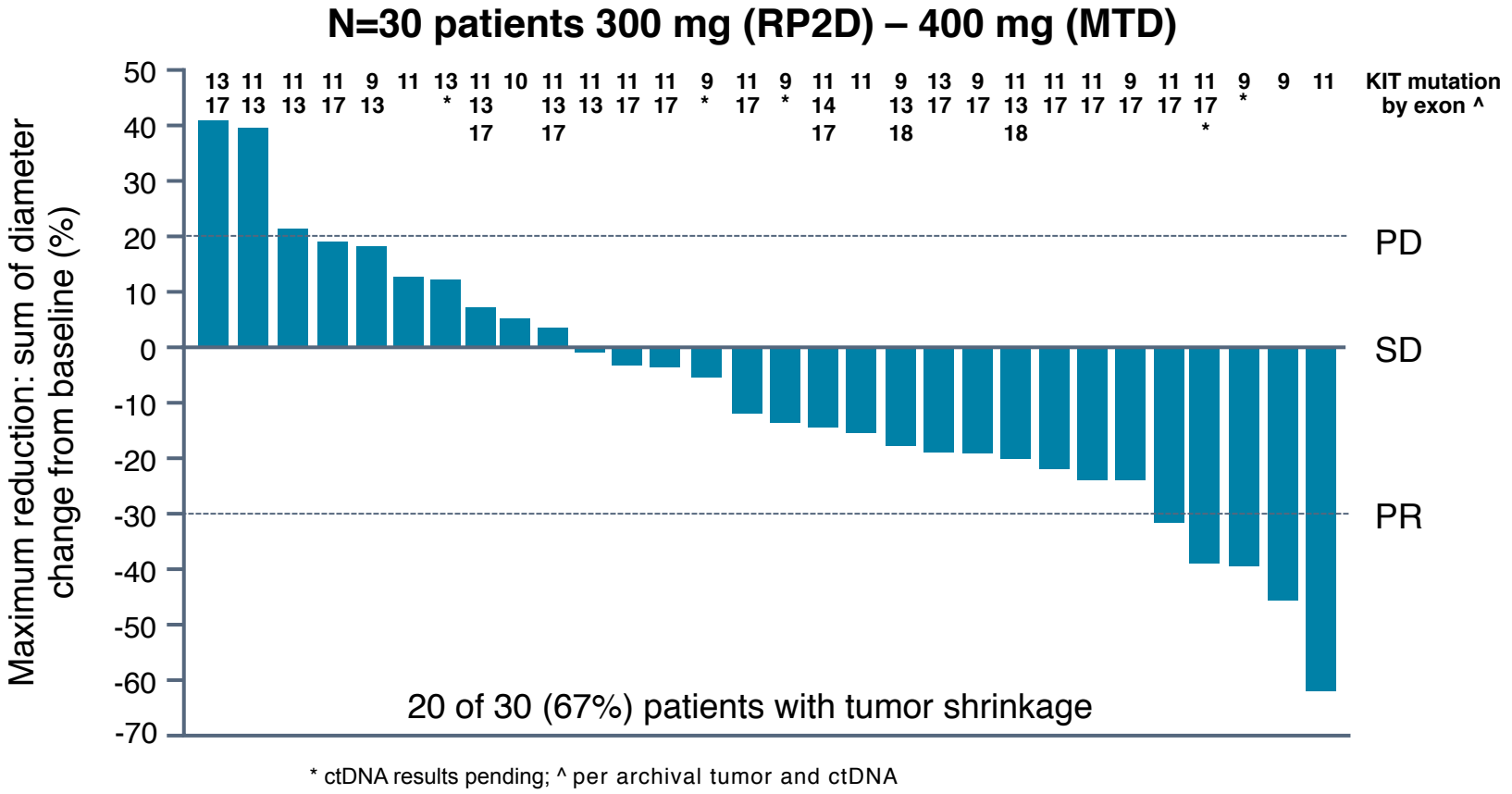
Unresectable GIST after imatinib and ≥1 other TKI (n=50)

Demography and baseline patient characteristics

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

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

Tumor reduction across multiple KIT genotypes (central radiology review)



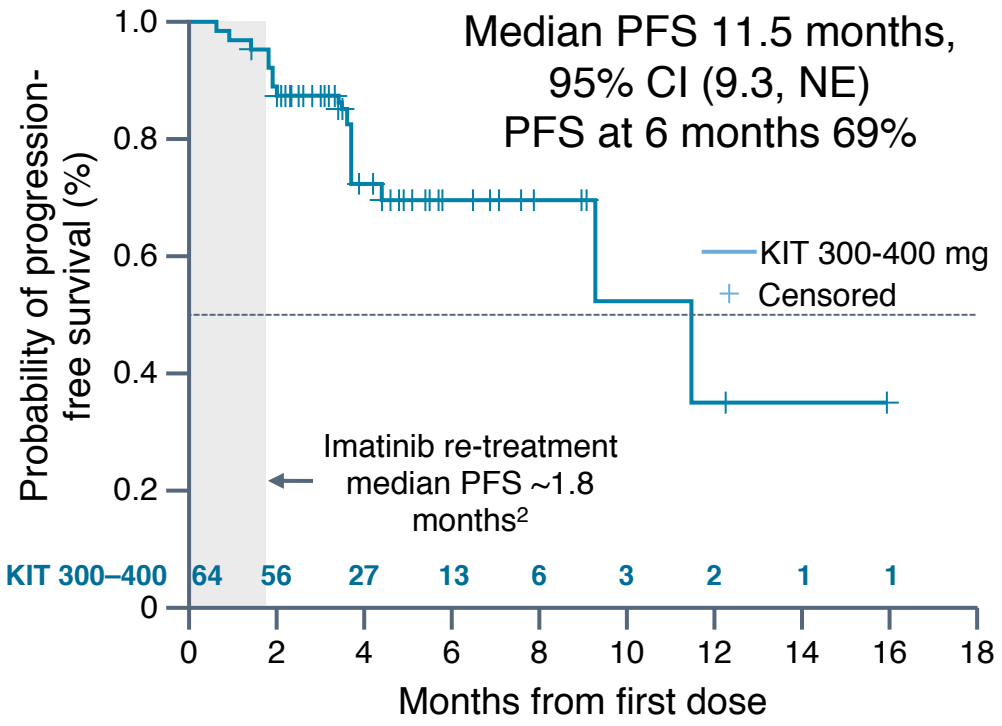
* ctDNA results pending; ^ per archival tumor and ctDNA

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

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

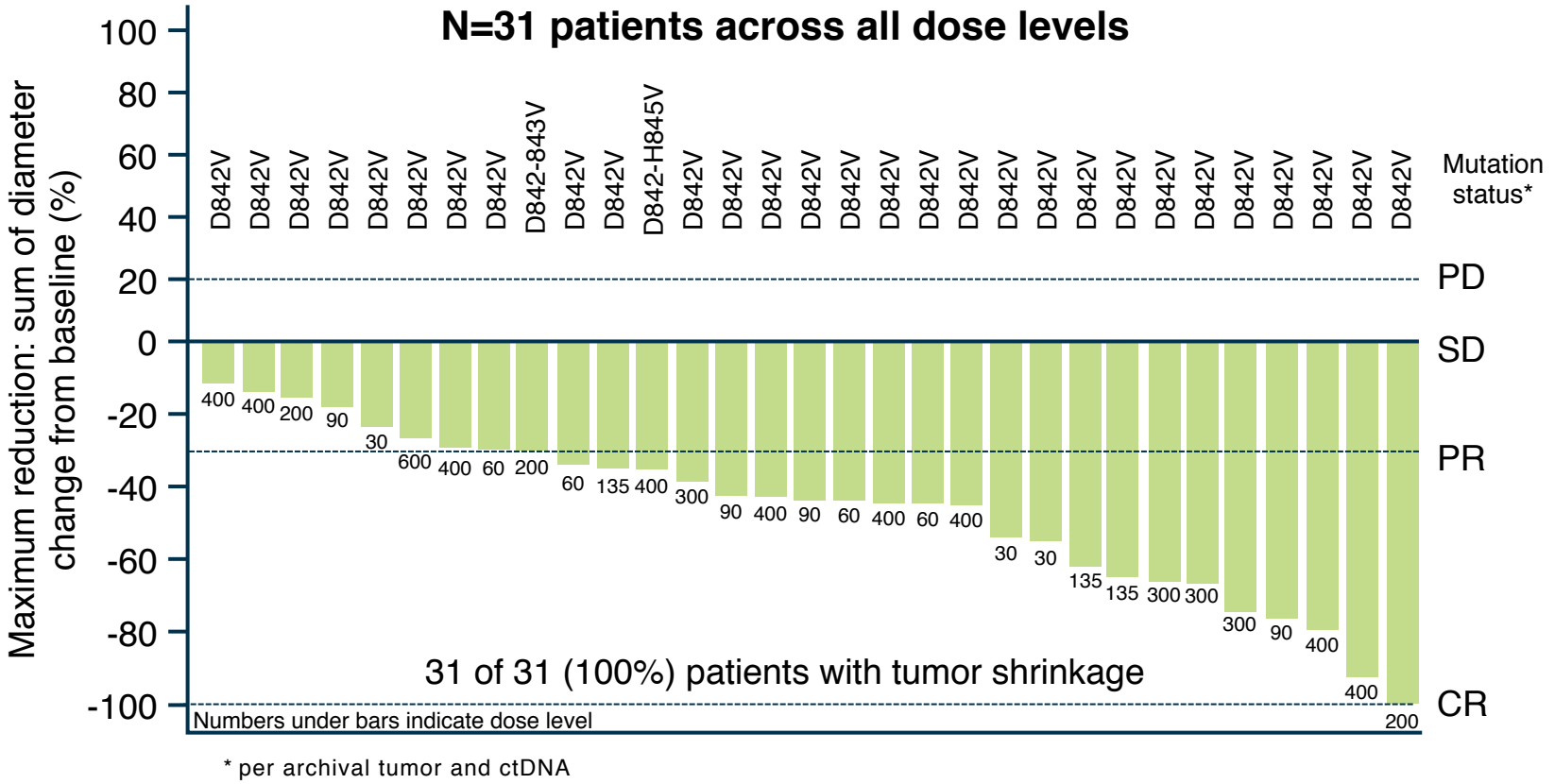
*300 RP2D–400 MTD mg; ^2 pending confirmation

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



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

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



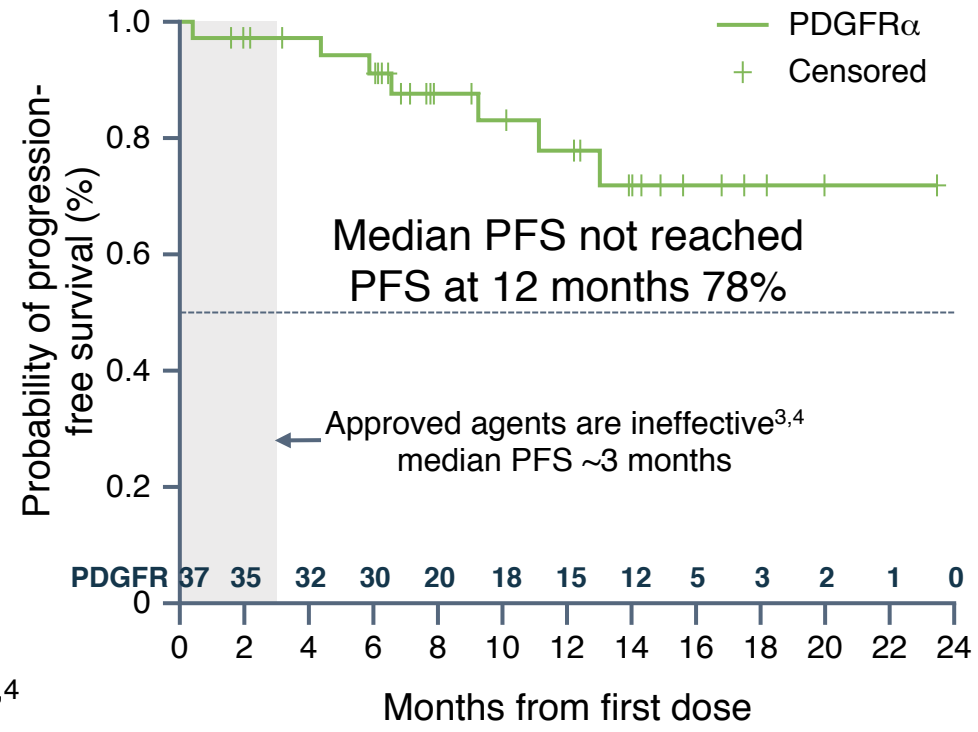
PDGFRα D842-mutation is in the activation loop!

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

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

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

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



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

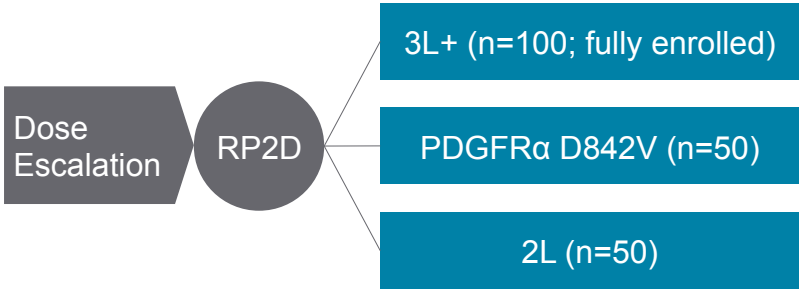
Avapritinib has potent, clinically important activity in GIST

- Remarkable response rates and prolonged PFS in PDGFRα-driven GIST may support expedited path for FDA approval
- Response rate and prolonged PFS in heavily pretreated KIT-driven indicated important activity in patients with drug-resistant KIT-mutant GIDT
- Based on these encouraging data:
  - Second-line expansion cohort has been added and is enrolling
  - Phase 3 randomized study comparing avarpritinib to regorafenib in third-line GIST has started (first patient, May 2018)

Ongoing and planned avapritinib clinical trials in patients with GIST

NAVIGATOR

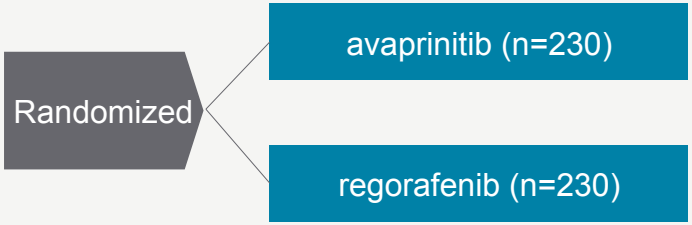
Phase 1
Advanced GIST



- Primary endpoints: ORR, safety
- Currently enrolling expansion

VOYAGER

Global Phase 3
3L advanced GIST



RP2D, recommended part 2 dose.

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
Making Cancer History®

DANA-FARBER CANCER INSTITUTE

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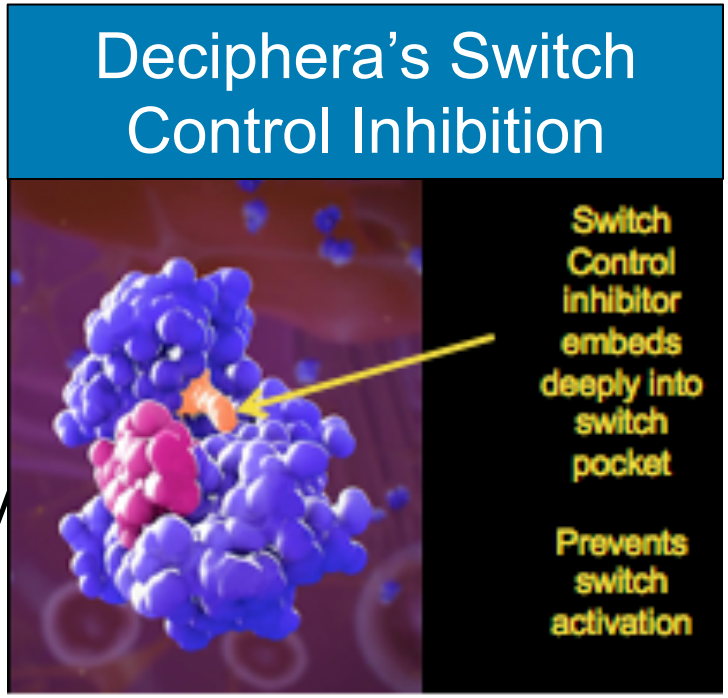
DCC-2618 BACKGROUND

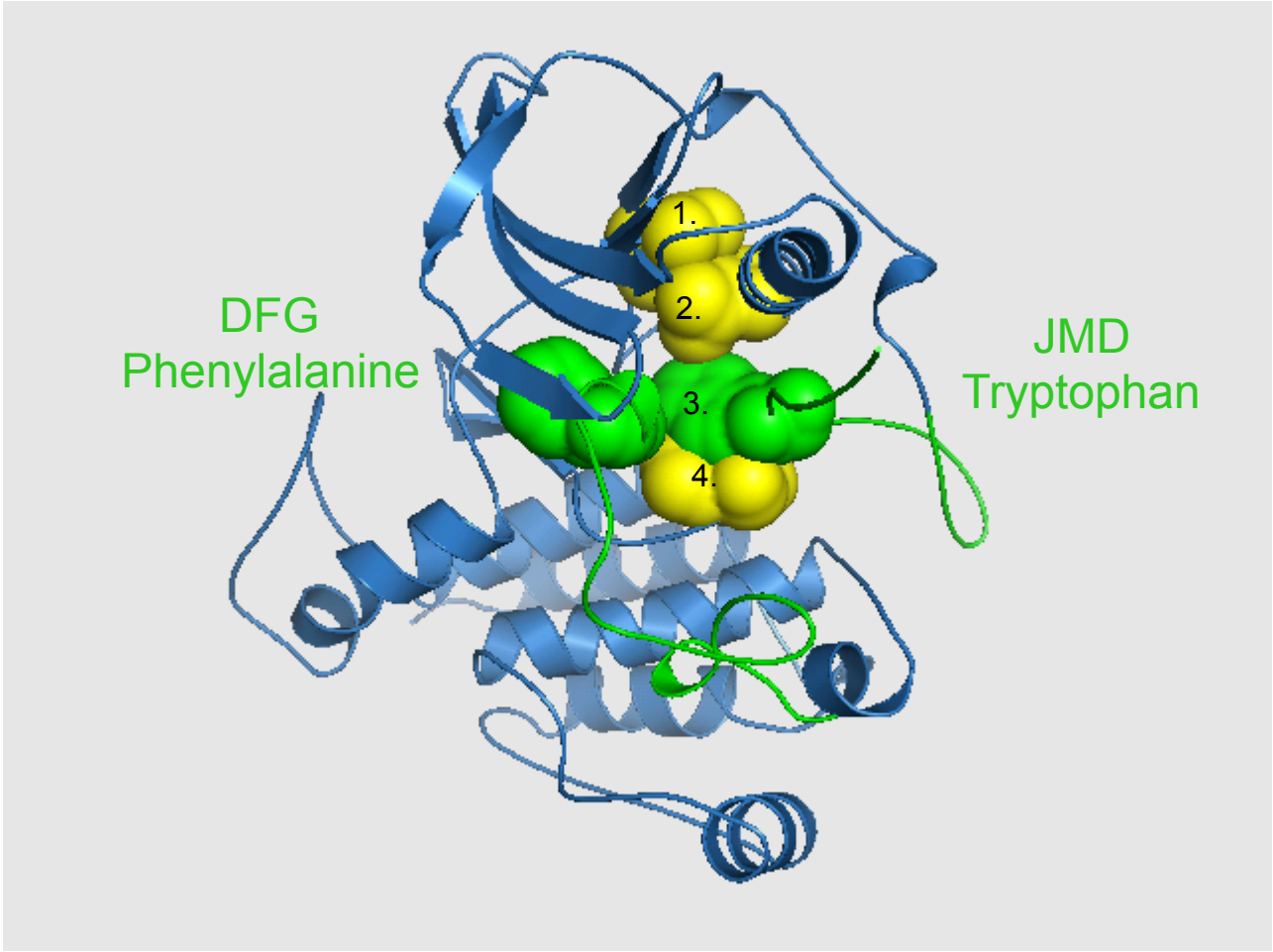
- DCC-2618 is a *KIT* and *PDGFRA* inhibitor resilient to gain-of-function and drug resistance mutations
  - Potency independent of ATP concentration



- 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*

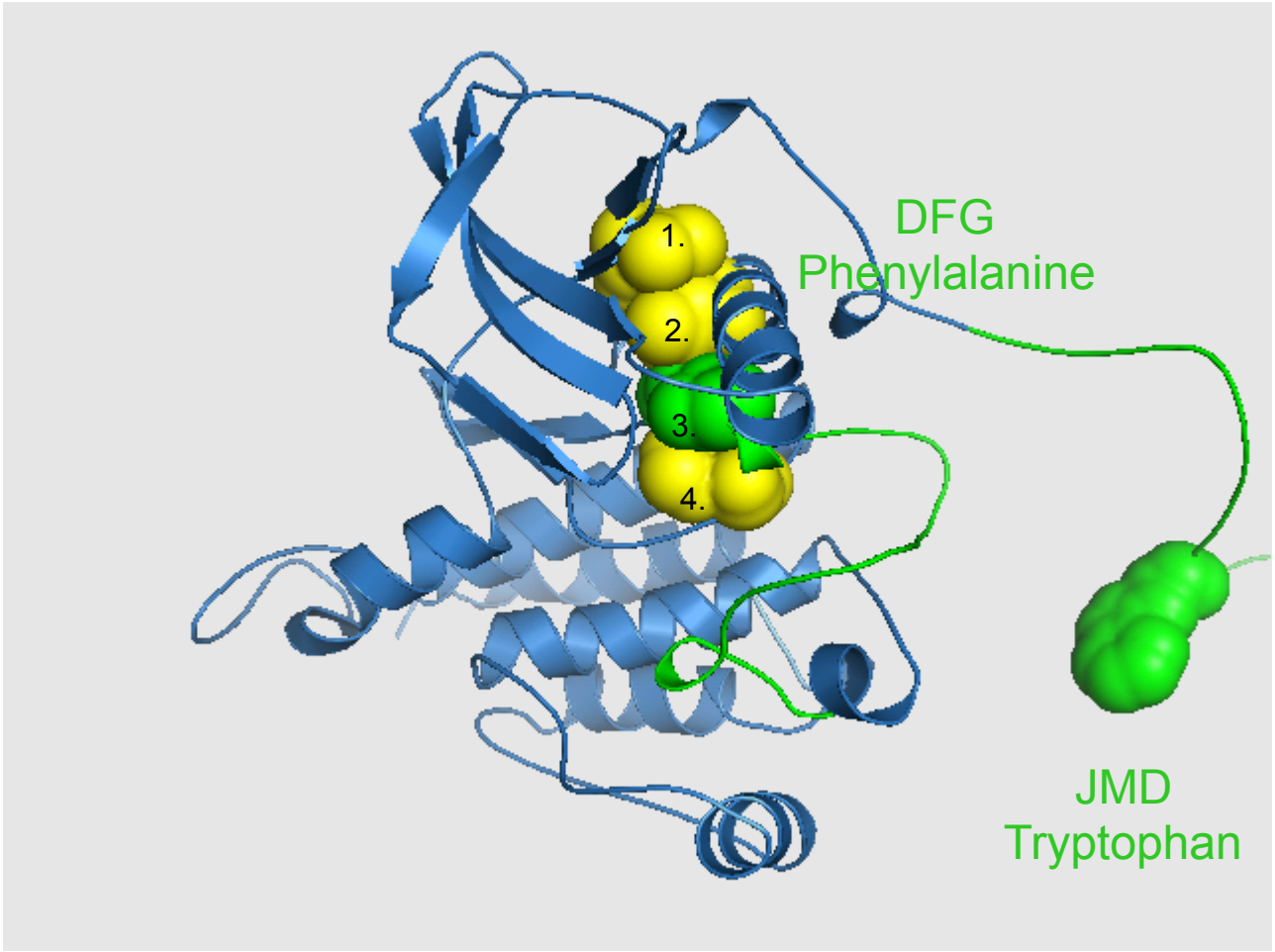
JM-Inhibited Inactive Kinase



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.

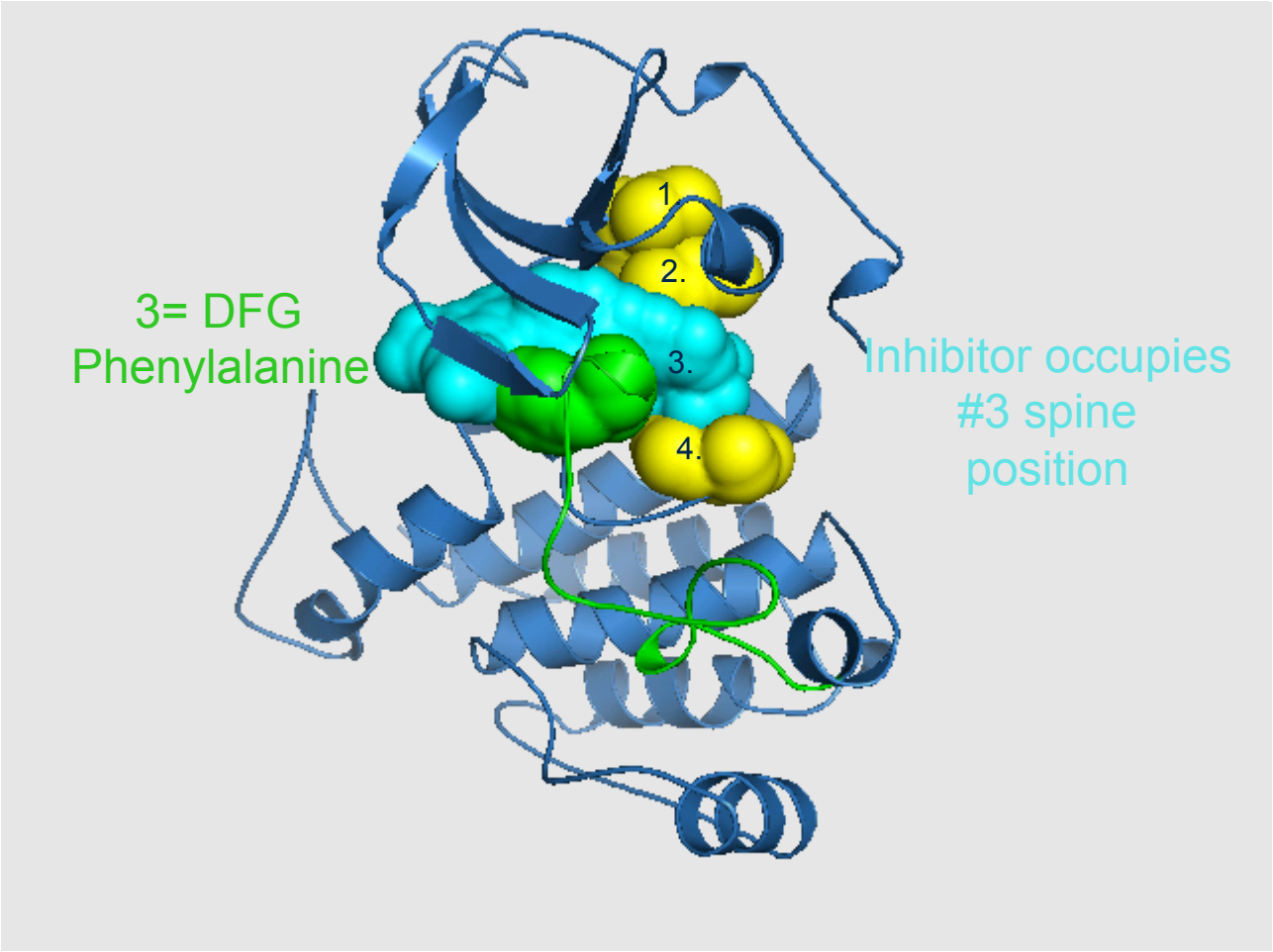
Activated Kinase Structure



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

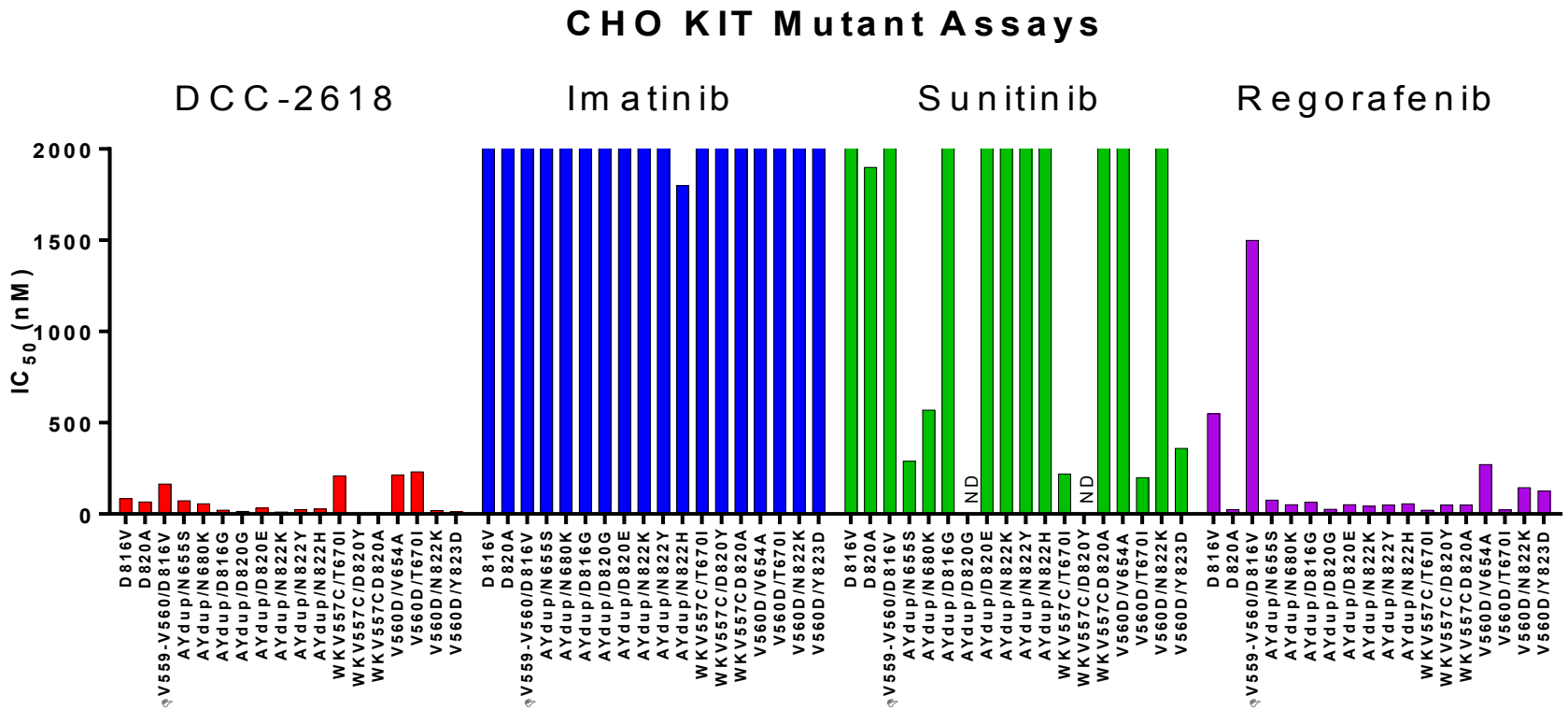


Snapshot 5. Switch Pocket Inhibitor binds to mutant KIT, with part of the inhibitor structure (blue) occupying the #3 position of the spine. This binding mode provides a biomimetic surrogate for the deleted inhibitory switch of mutant KIT.

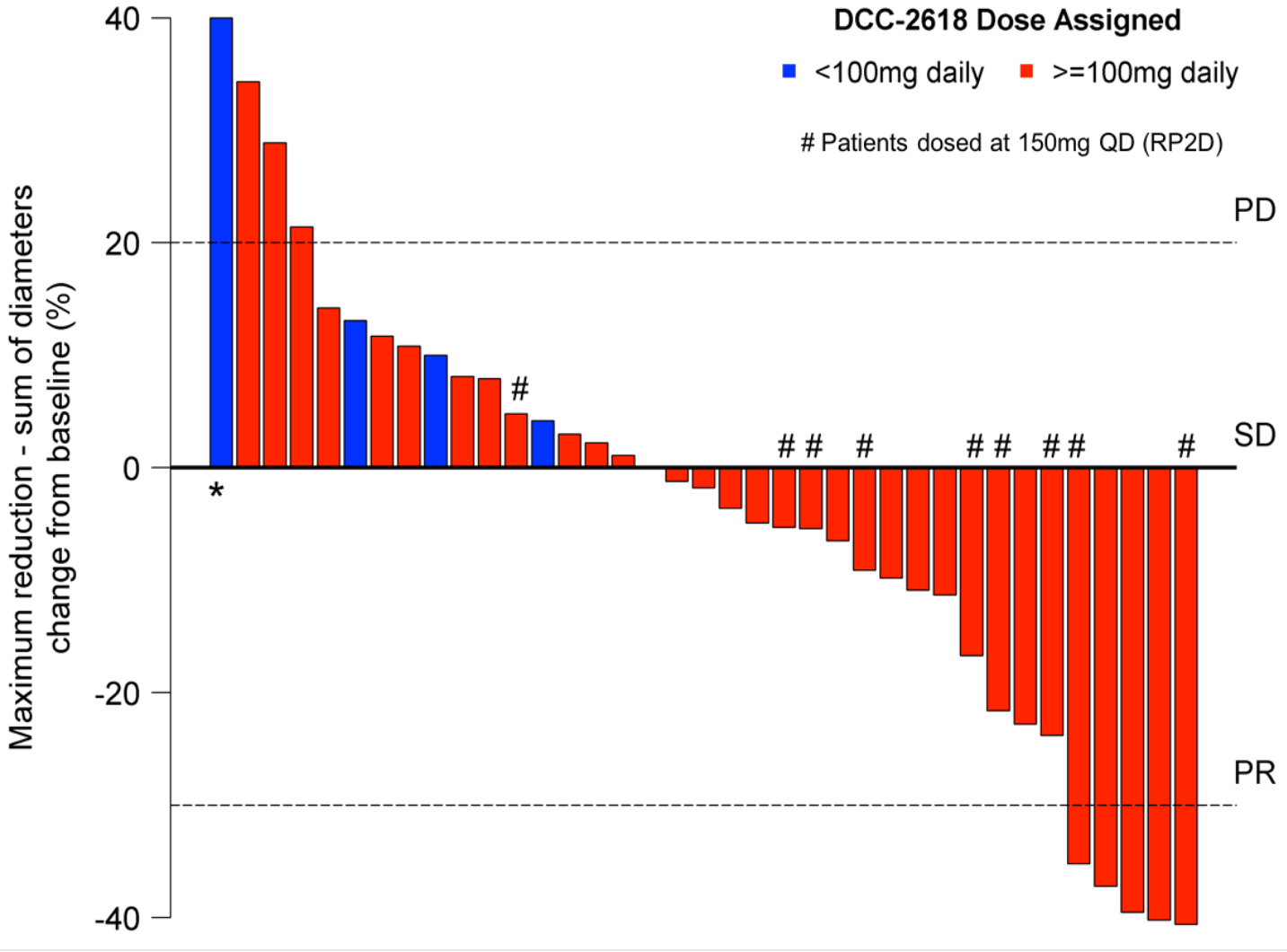
The 'DFG' phenylalanine residue (green) is forced to occupy the out/ inhibited conformation.

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



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

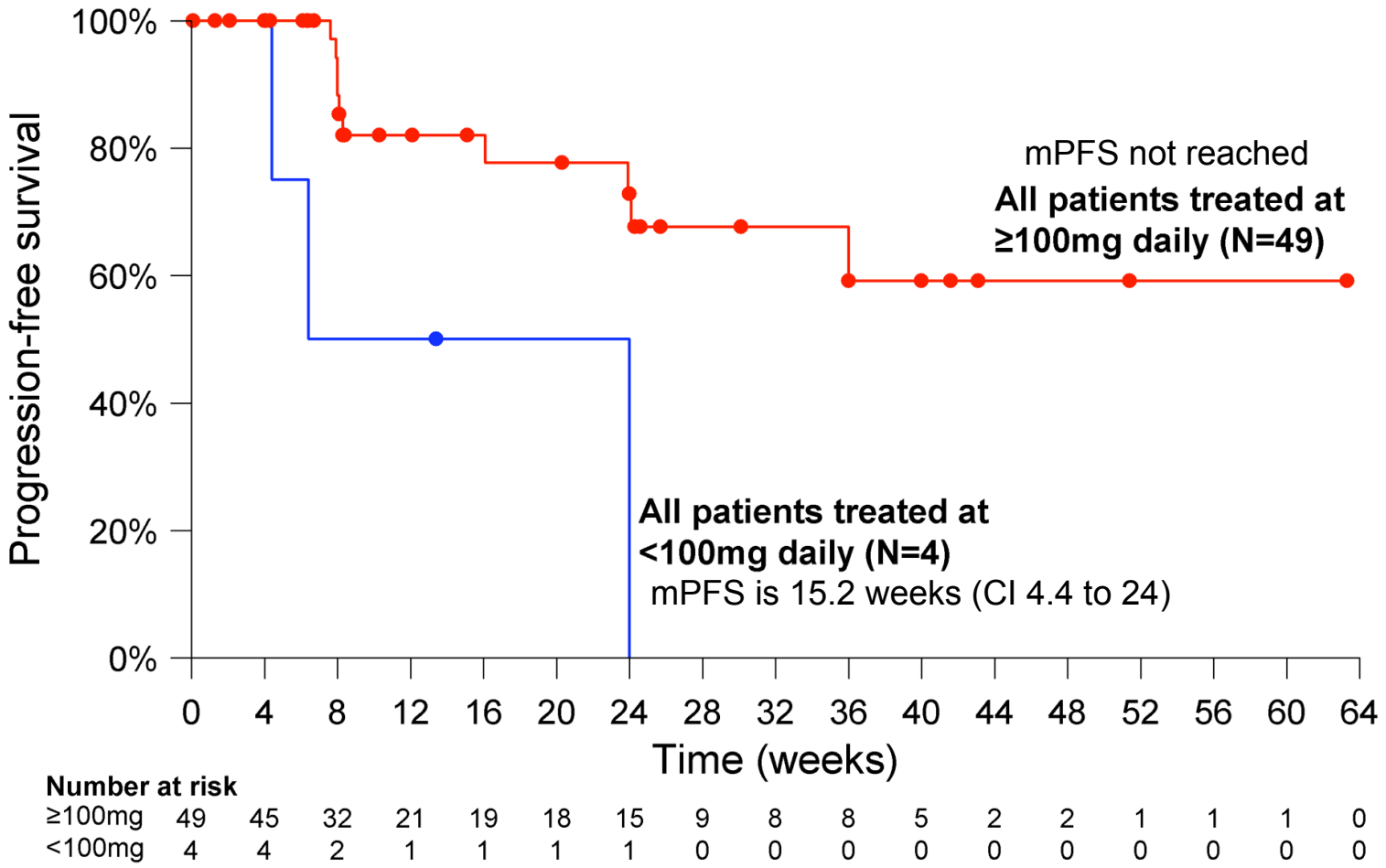


PD = Progressive disease, SD = Stable disease, PR = Partial response

*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

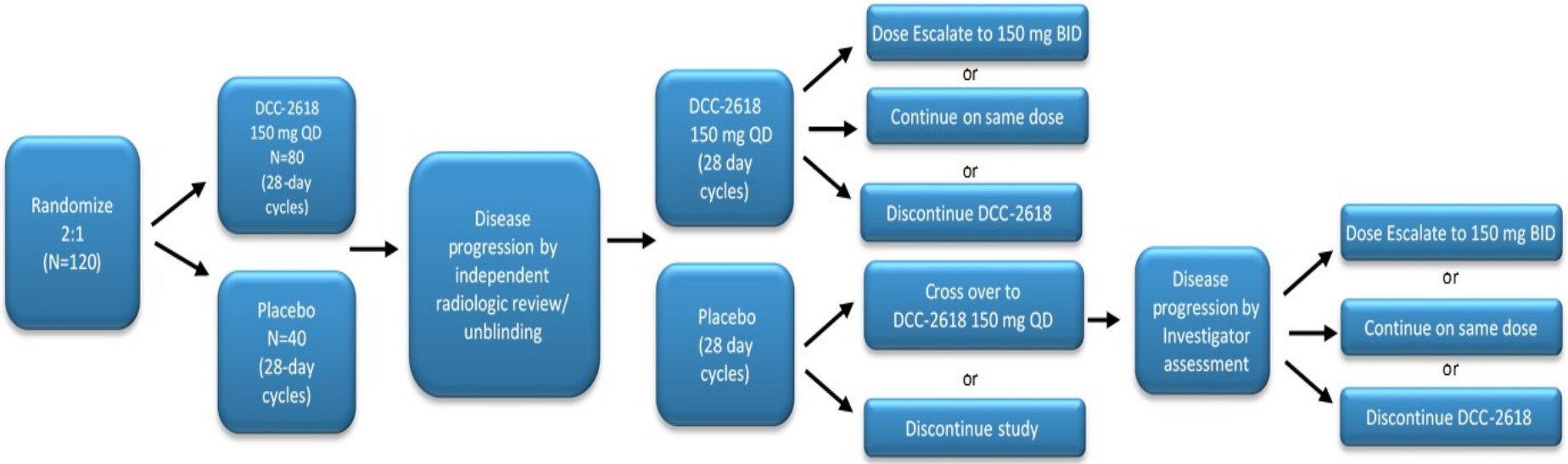


- Despite small sample size results suggest that doses of 40 or 60 mg/d are insufficient
- The fact that 30 mg BID is an insufficient dose is supported by improvement in disease control in a patient with PD after 24 weeks following dose escalation (not shown)

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

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

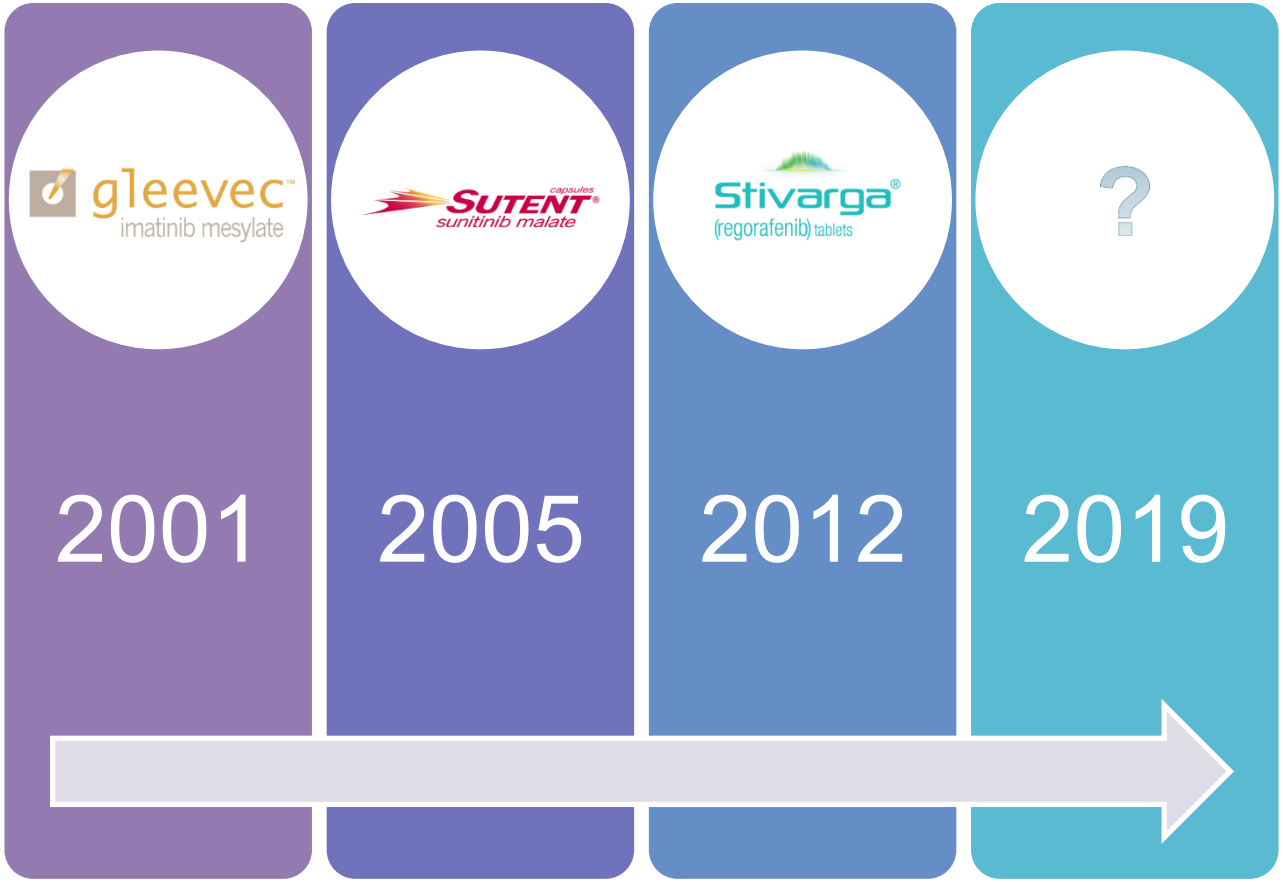
decīphera

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 the pivotal Phase 3 trial in second-line GIST, we will 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

Avapritinib and DCC-2618 Clinical Studies

- Avapritinib and DCC-2618 are novel potent KIT inhibitors with unprecedented activity against KIT exon 17 mutations
- Both drugs appear safe and tolerable and have moved from dose-escalation to dose-expansion phase and more recently to open or planned phase 3 studies
- Currently there are two open phase 3 studies:
  - regorafenib vs. avapritinib (third- or fourth-ilne)
  - DCC-2618 vs. placebo (fourth-line or later)
- Coming soon: phase 3 of DCC-2618 vs. sunitinib (second-line)
- Contact my study nurse (Tracy) at walkertr@ohsu.edu or 503-346-1183 if you are interested in being considered for any of these studies


gleevec
imatinib mesylate
2001
SUTENT
capsules
sunitinib malate
2005
Stivarga
(regorafenib) tablets
2012
?
2019

Summary

- In the past 10 years, there have been tremendous advances in our understanding of GIST biology and pathology
- “Mutation, mutation, mutation”
- Exciting new drugs are being developed and seem poised to transform our treatment of imatinib-resistant GIST

Acknowledgements

- 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 avapritinib and DCC-2618 studies