New Approaches to Treatment of Gastrointestinal Stromal Tumor

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Outline

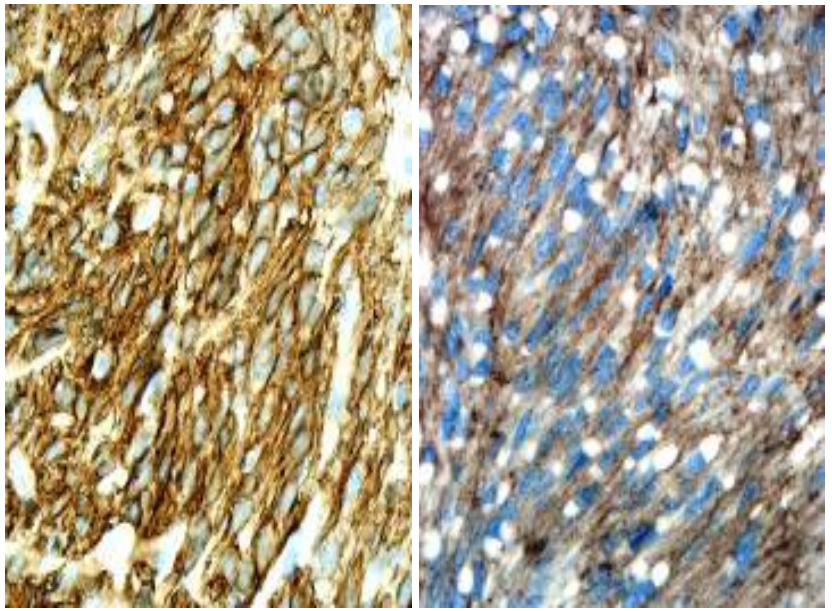
- The GIST Basics
- Approved treatments
- New approaches

THE GIST BASICS

Mazur and Clark, 1983

Coined the term **Gastrointestinal stromal tumors**

Some **smooth muscle tumors of the GI tract** "expressed **neural crest antigens** such as S-100 protein and neuron-specific enolase"



GIST

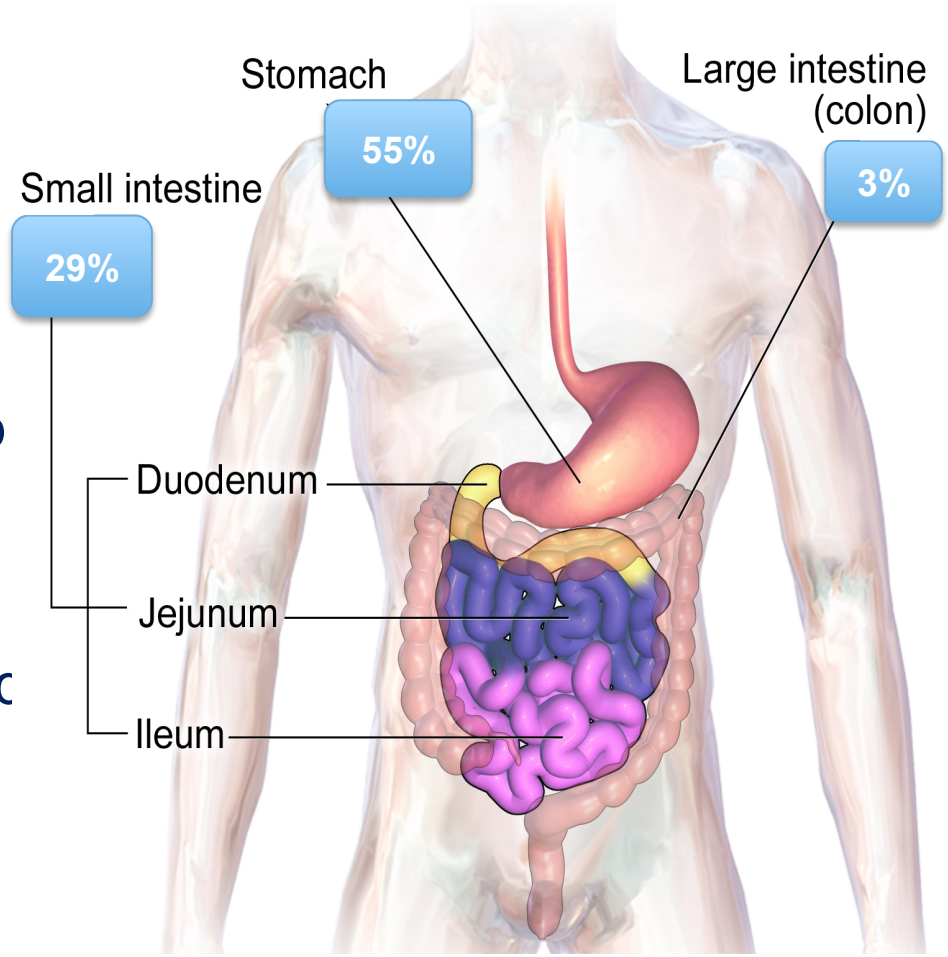
Most common GI sarcoma

- Arises from Interstitial cell of Cajal or precursor cell
- 0.2% of all GI tumors, but 80% of GI sarcomas
- Can arise anywhere along GI tract (stomach>small intestine>others)

Most commonly diagnosed in the 40-60 year age group

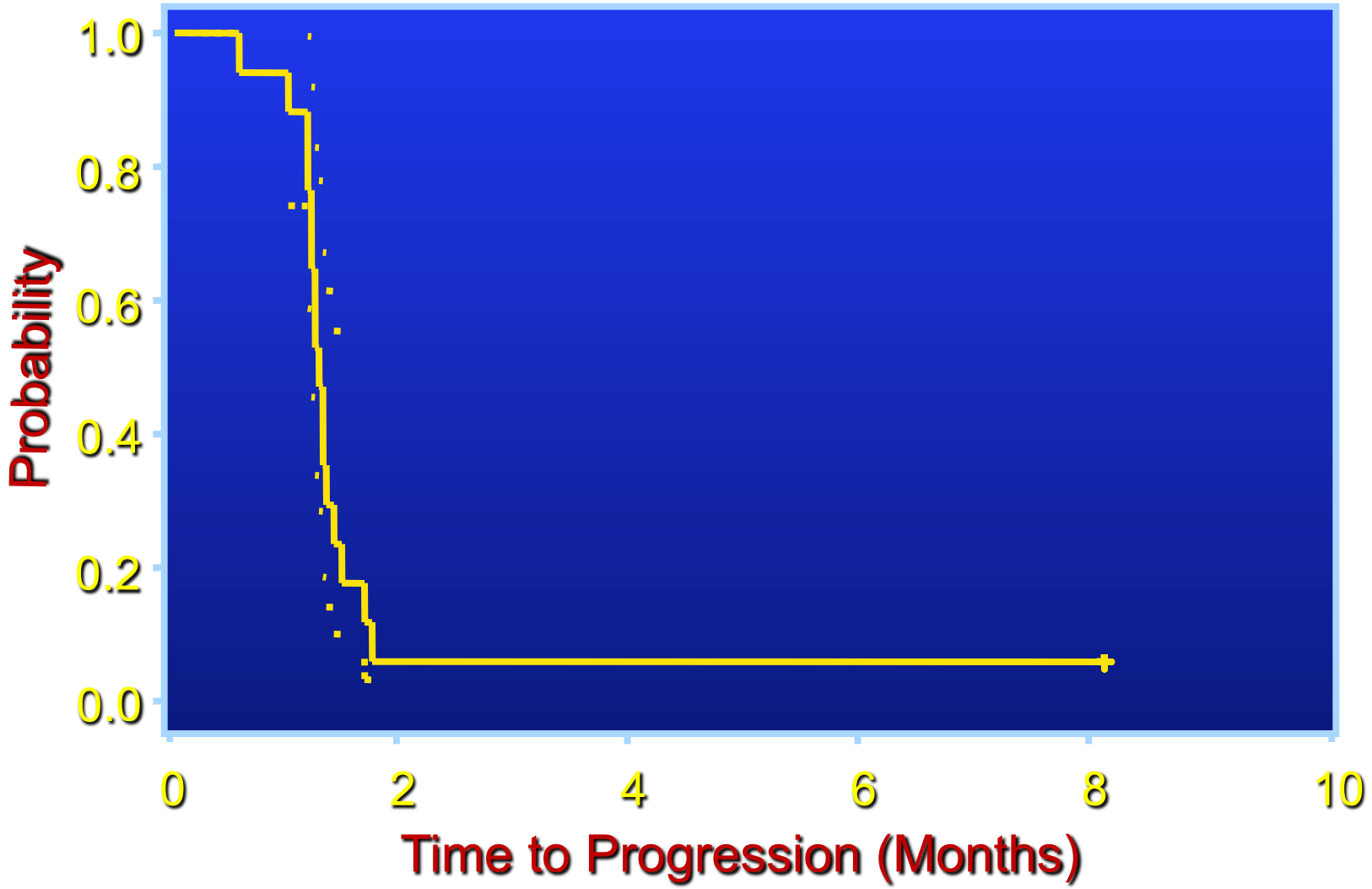
- Similar male/female incidence, although some reports suggest a slightly higher incidence in men

GIST have an incidence of 14.5 per million annually and a prevalence of 129 per million



Fletcher et al. Hum Pathol. 33:459; 2002.
Jemal et al. CA Cancer J Clin. 55:10, 2005.
Joensuu et al. Lancet Oncol. 3:655, 2002.
Miettinen et al. Pol J Pathol. 54:3, 2003.
Nilsson et al. Cancer.103:821, 2005.

Time to Progression on Chemotherapy



Courtesy of Demetri, G

Survival correlates with Resection Status

Primary tumor, completely resected	96 months
Primary tumor, **incompletely** resected	26 months
Recurrent disease, completely resected	49 months
Recurrent disease, **incompletely** resected	8 months
Metastatic disease, completely resected	39 months
Metastatic disease, **incompletely** resected	11 months

Cleary et al. Ann Surg Oncol, 2001

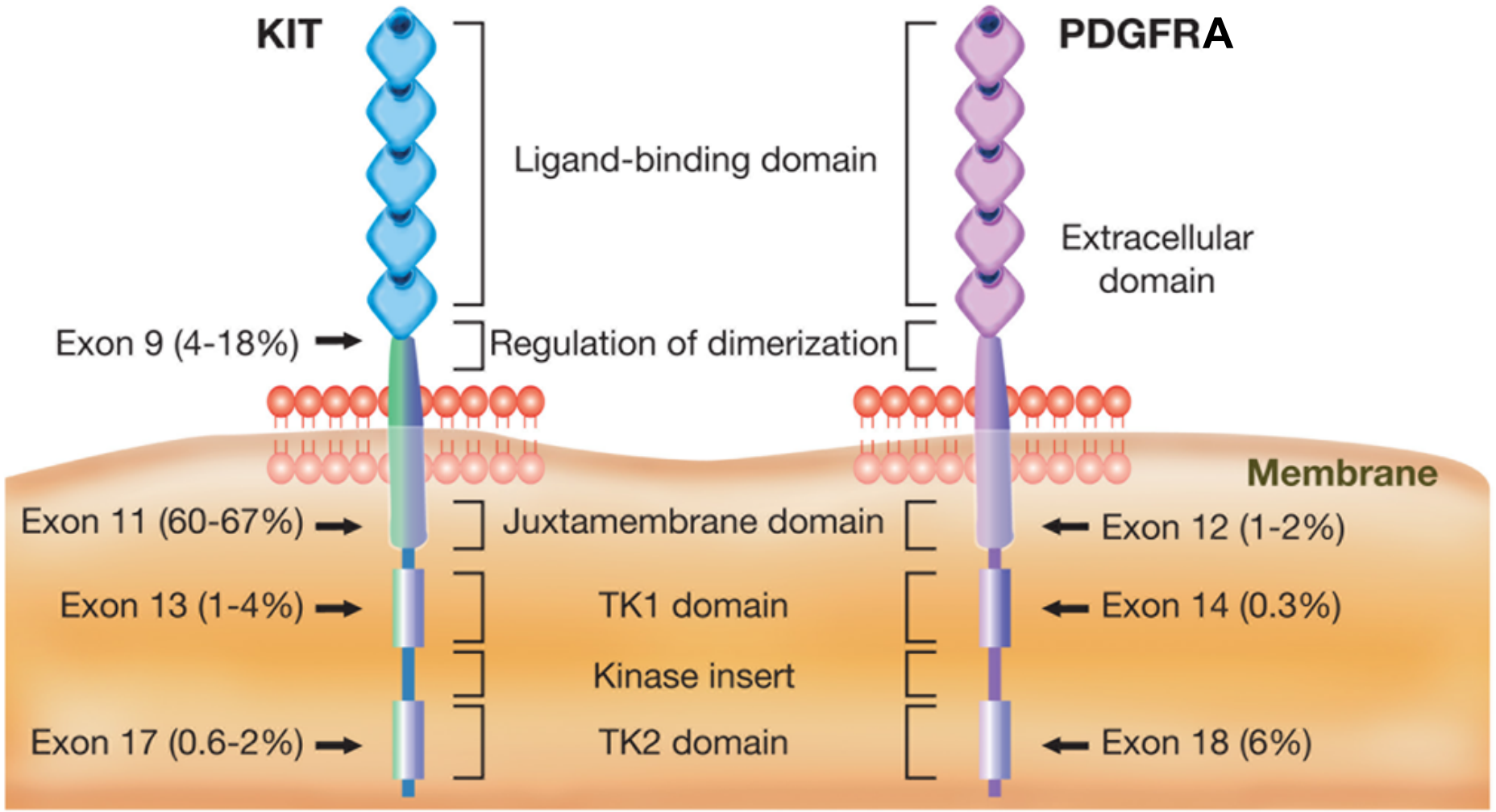
Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

Science 279:577-580, 1998

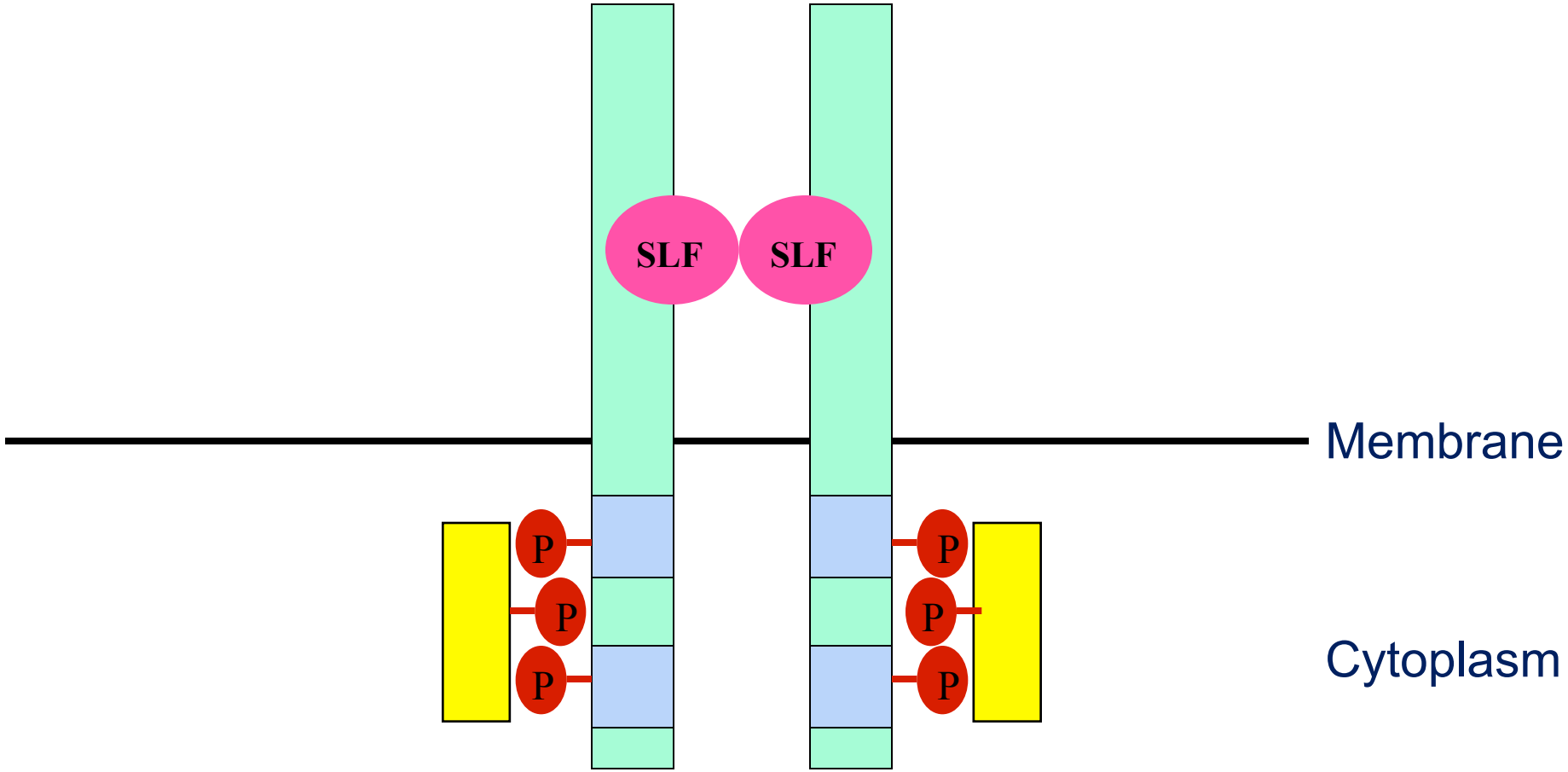
- 5 of 6 GIST had mutations in KIT gene
- Mutant forms of KIT are constitutively active
- Proposed that GIST may originate from ICCs
- Studies in knock-in mice with KIT mutations
  - Demonstrated that constitutive KIT signaling is sufficient to induce GIST
  - Parallel with the pathology seen with familial KIT mutations, eg. mastocytosis

Frequency of Mutation in *KIT* and *PDGFRA*

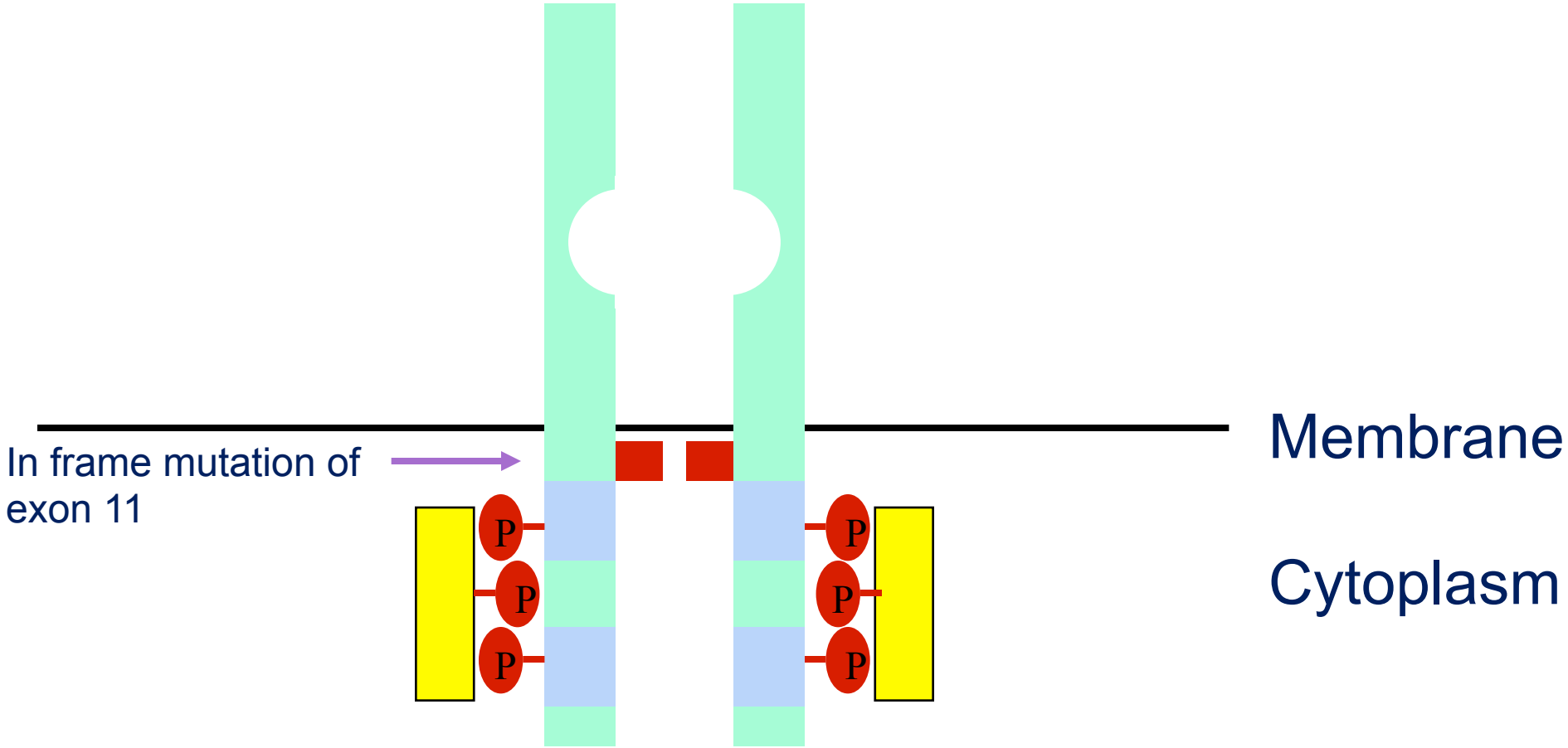


Tarn & Godwin, *Curr Treat Options Oncol*, 2005

Ligand-dependent Activation of Wild-type KIT

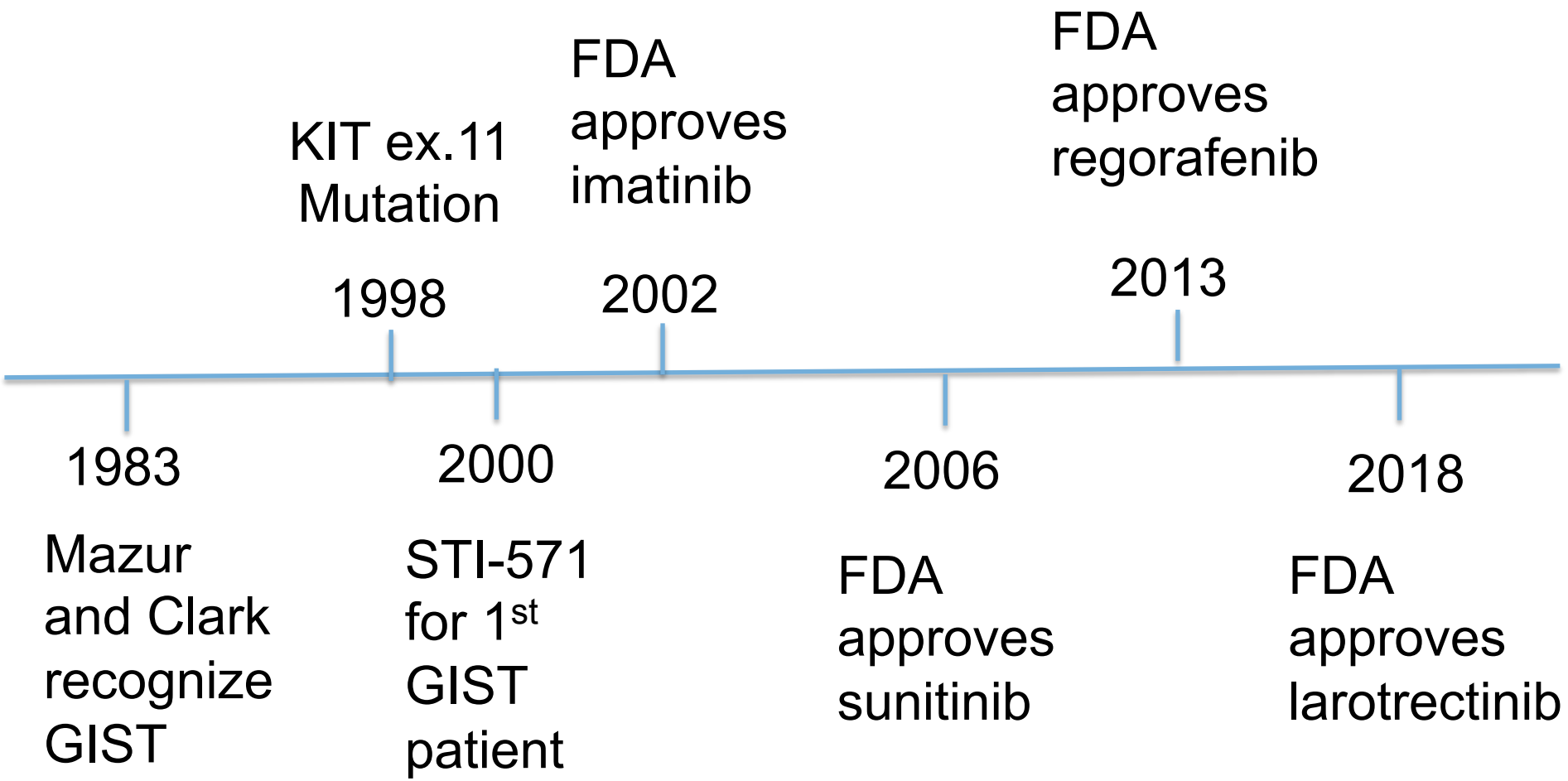


Ligand-independent Activation of Mutant KIT



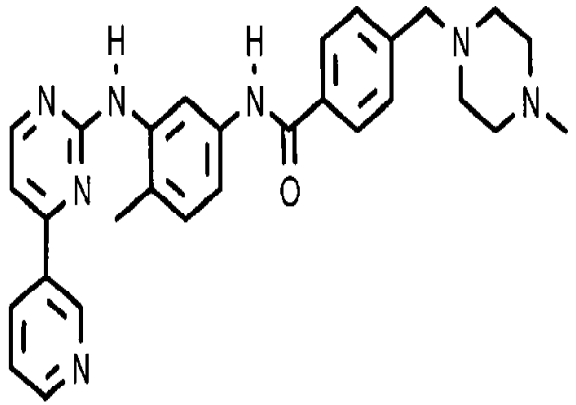
APPROVED AGENTS

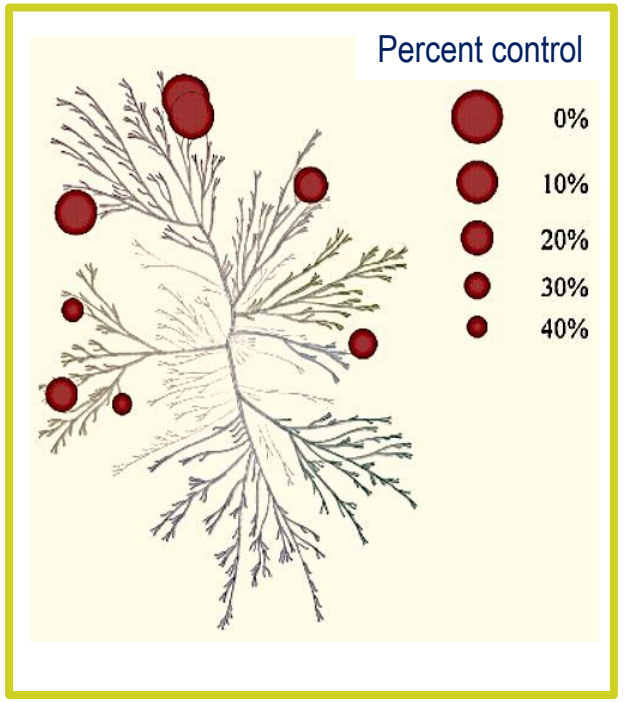
Drug Approval Time Line



Imatinib mesylate (STI-571, Gleevec)

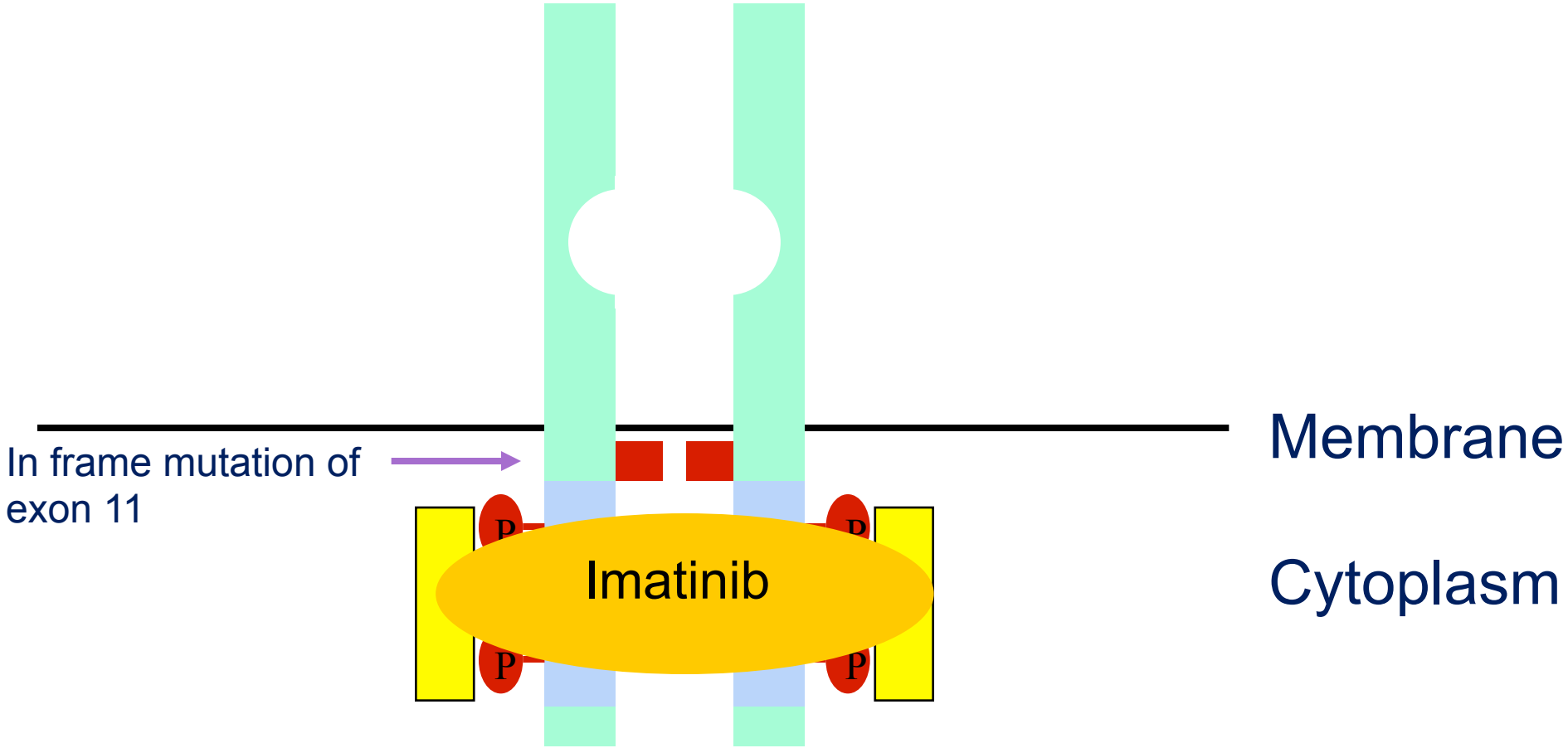
- Identified in a screen for tyrosine kinase inhibitors
- Synthesized compound was optimized for inhibition for specific kinases
- Competitively inhibits the ATP-binding site of the enzyme and leads to inhibition of phosphorylation of down stream signals
- Has activity against KIT and PDGFRA mutations





Murphy EA *et al. PNAS* 2010; 107: 4299–4304

Ligand-independent Activation of Mutant KIT



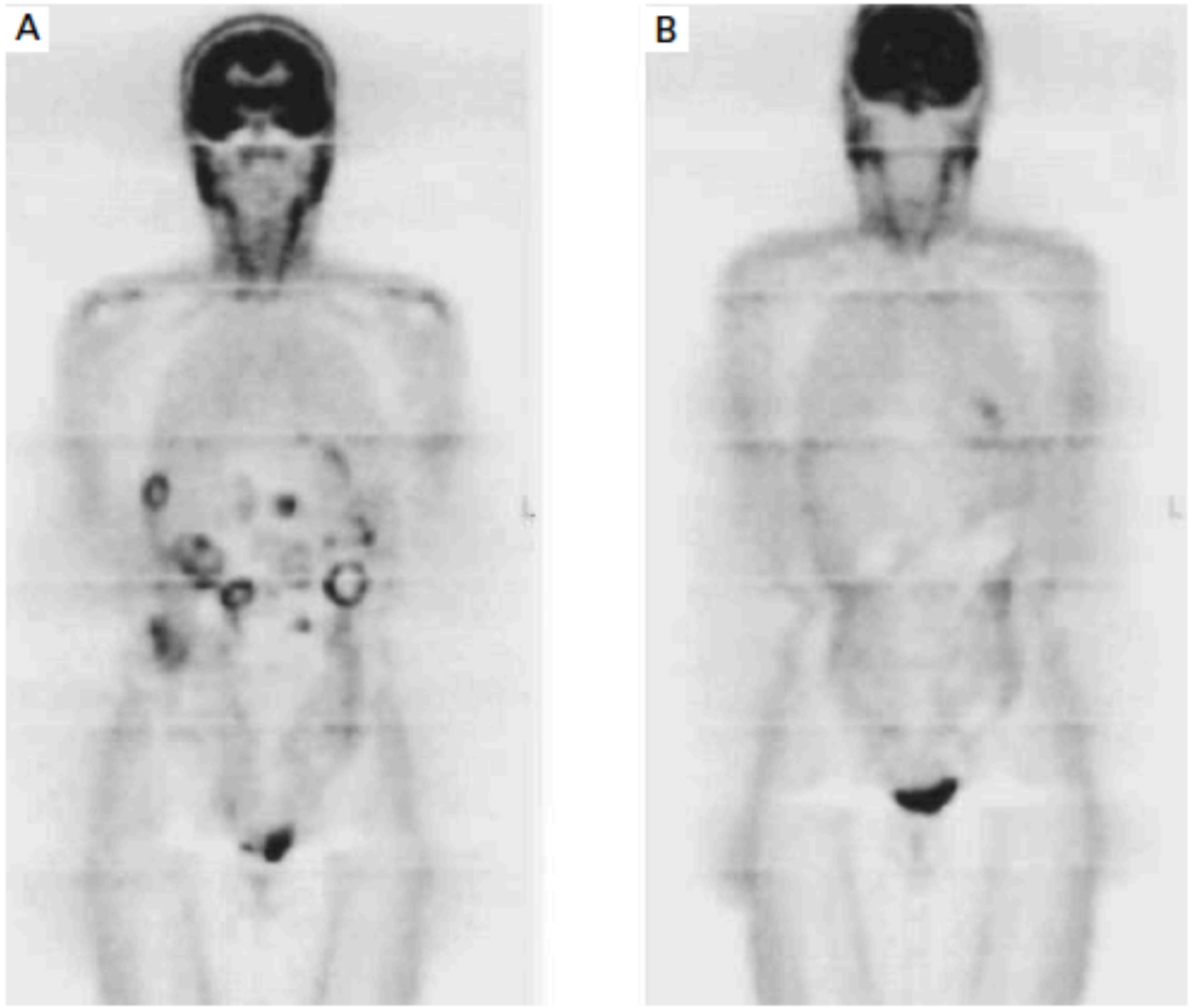


Figure 2. PET Studies with [^{18}F]Fluorodeoxyglucose as the Tracer.

Before STI571 therapy (Panel A), there were multiple metastases in the liver and upper abdomen. There was also marked retention of [^{18}F]fluorodeoxyglucose in the right renal pelvis and ureter, a finding indicative of hydronephrosis. After four weeks of treatment (Panel B), there was no abnormal uptake of tracer in the liver or right kidney.

Joensuu et al. N Engl J Med. 2001. 5;344(14):1052-6.

Response data for Imatinib

Dose	CR (%)	PR (%)	SD (%)	PD (%)	NE/unknown (%)
400 mg daily	0-5	40-68.5	13.7-32	12-15.1	2.7-10
300 mg BID	2.7	64.9	17.6	8.1	6.8
400 mg BID	3-6	42-48	22-32	10-9	5-15
500 mg BID	0	57	29	14	0

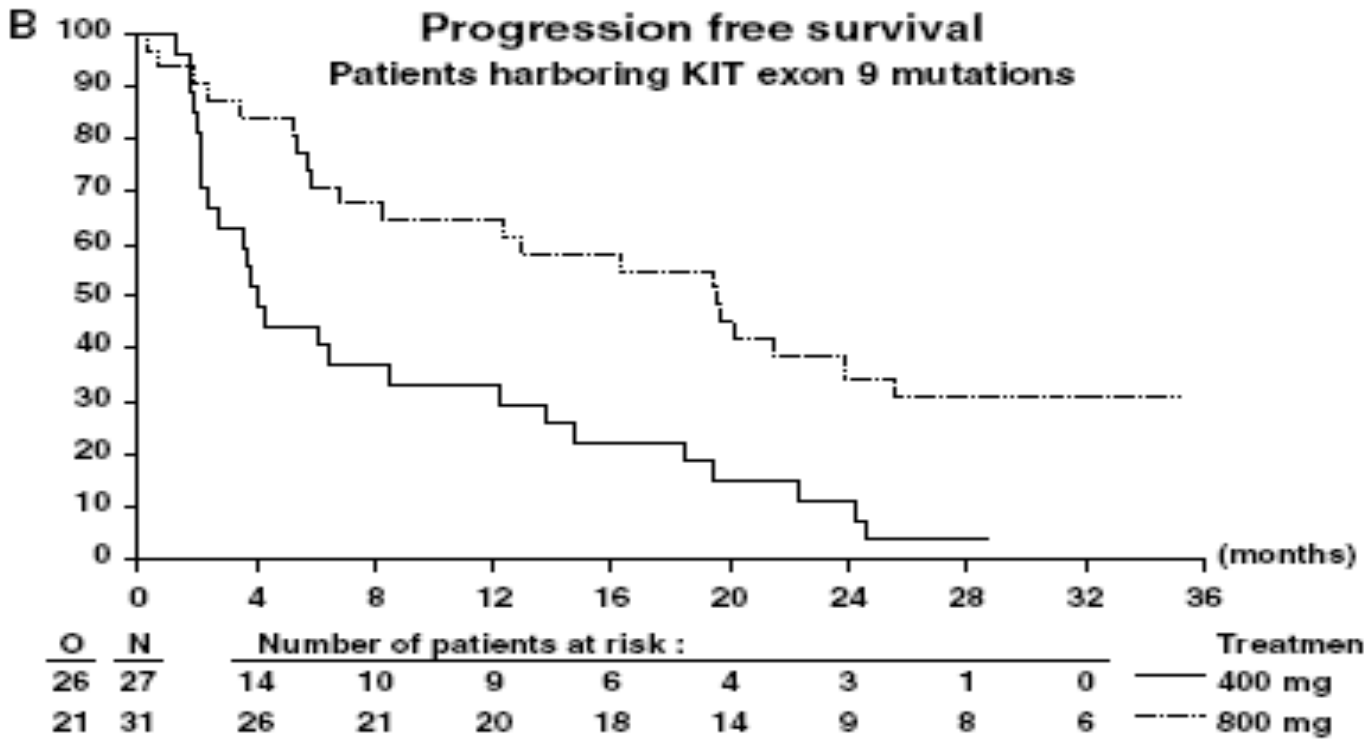
van Oosterom A et al. Lancet 2001 and Eur J Cancer, 2002.
Demetri G et al. NEJM, 2002.
Verweij J et al. Eur J Cancer 2003 and Lancet, 2004.
Blanke CD et al. JCO, 2008.

Functional Resistance: Phase III data

	KIT mutants				PDGFRA mutants	Wild type	Total
Response	Exon 9	Exon 11	Exon 13	Exon 17			
CR	3 5.17%	16 6.45%	0 -	0 -	0 -	0 -	19 5.04%
PR	17 29.31%	152 61.29%	4 66.67%	2 66.67%	3 30.00%	12 23.08%	190 50.40%
NC	27 46.55%	63 25.40%	2 33.33%	1 33.33%	3 30.00%	26 50.00%	122 32.36%
PD	**10** **17.24%**	**8** **3.23%**	**0** **-**	**0** **-**	**4** **40.00%**	**10** **19.23%**	**32** **8.49%**
Uneval.	1 1.72%	9 3.63%	0 -	0 -	0 -	4 7.69%	14 3.71%
Total	58	248	6	3	10	52	377

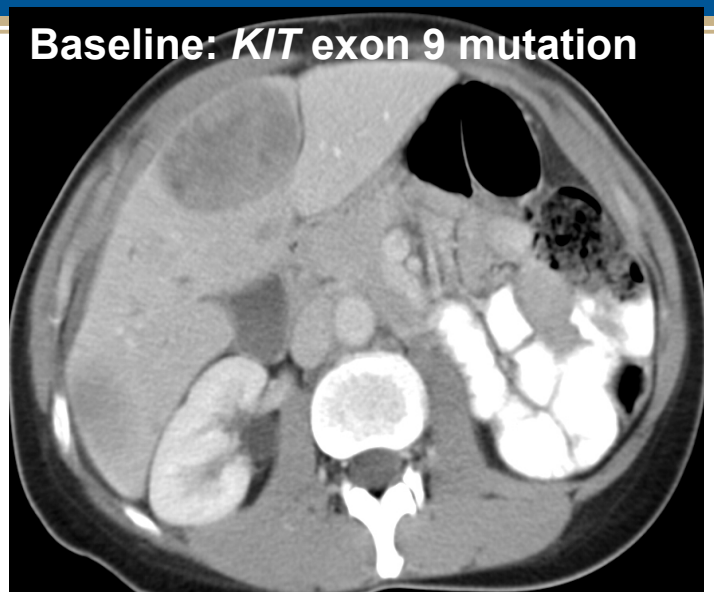
Debiec-Rychter et al. Eur J Cancer. 2006

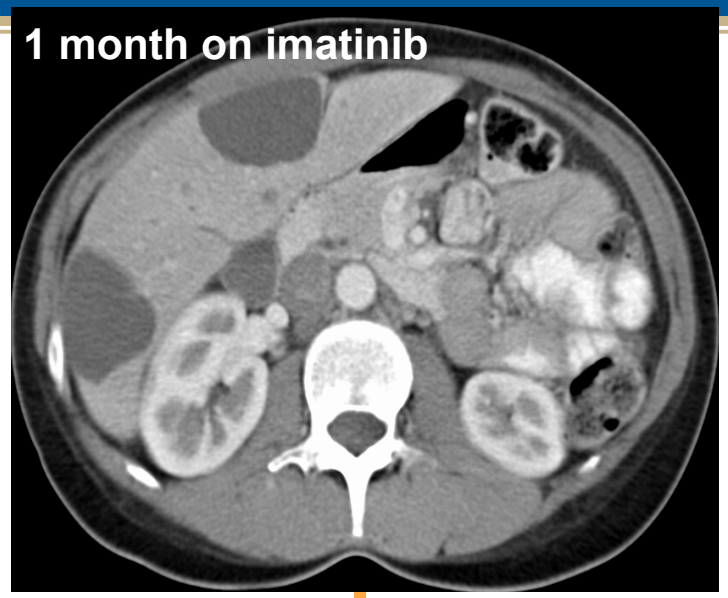
High Dose Imatinib improves PFS for Exon 9



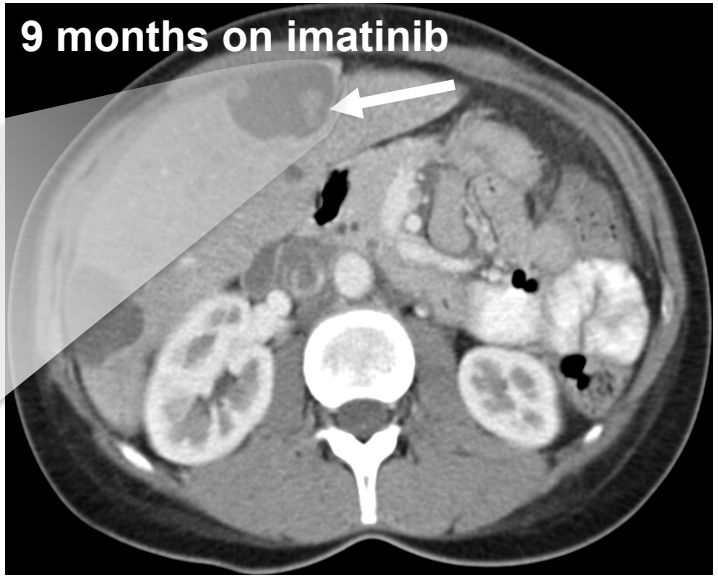
Debiec-Rychter et al. Eur J Cancer. 2006

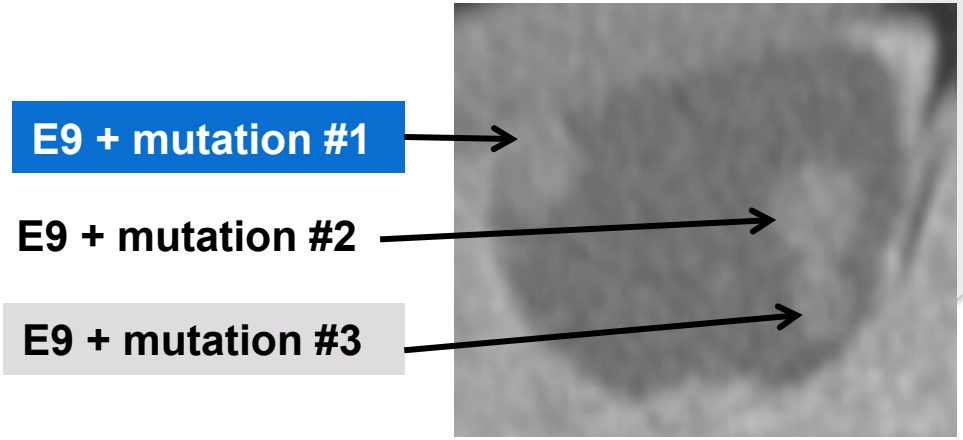
Secondary Resistance: Clonal Evolution





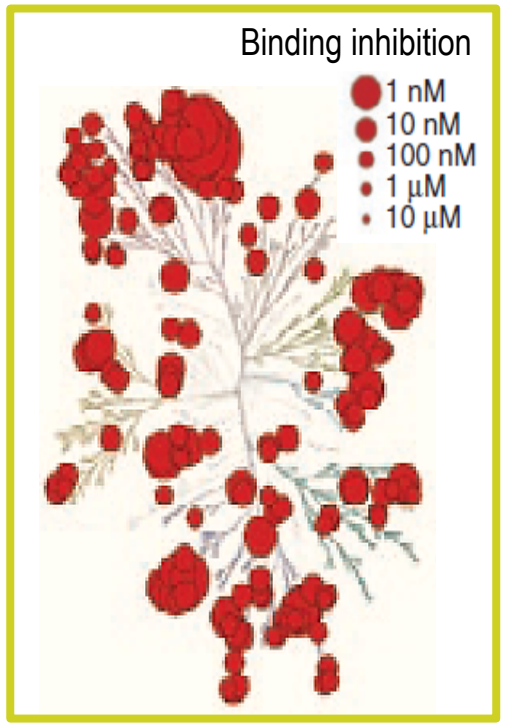
Response in GIST followed by SECONDARY resistance

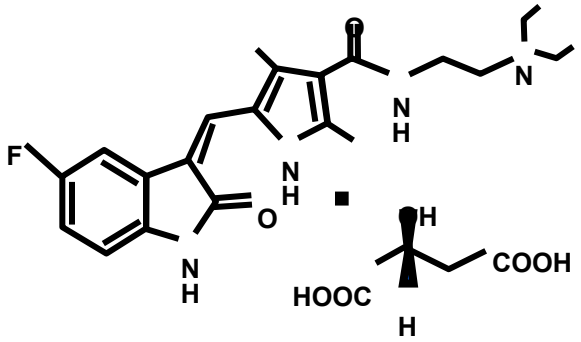




Demetri et al ASCO 2013

Sunitinib: Multi-targeted Receptor Tyrosine Kinase Inhibitor





Enzymatic K_i (µM)

PDGFR-β	VEGFR-2	VEGFR-3	FGFR1	EGFR
0.008	0.009	0.017	0.83	>10

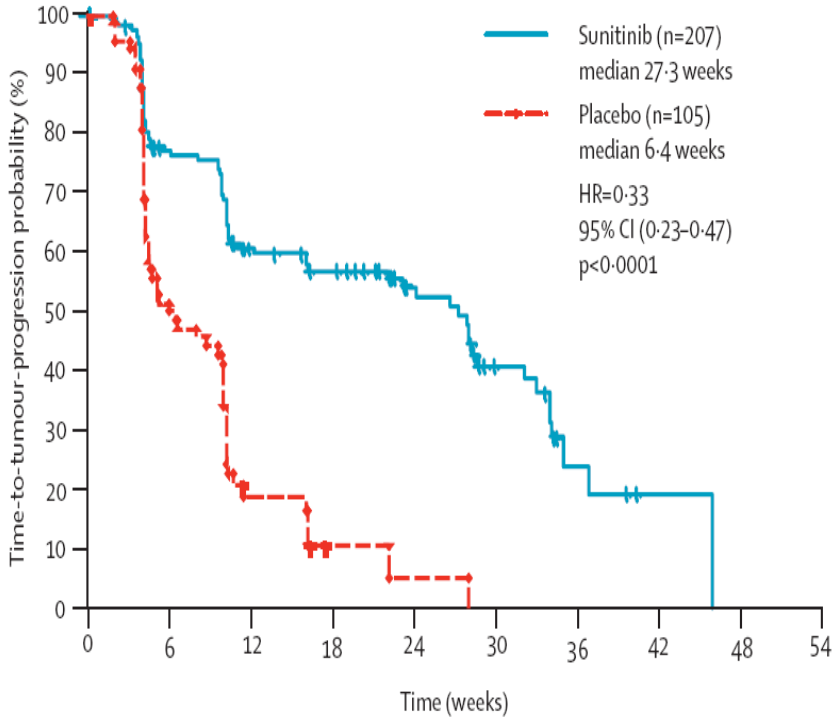
Cellular IC_{50} (µM)*

PDGFR-β	VEGFR-2	KIT	FLT3 (WT)	EGFR	MET
0.008	0.009	0.01	0.25	8.9	12.0

*Receptor phosphorylation

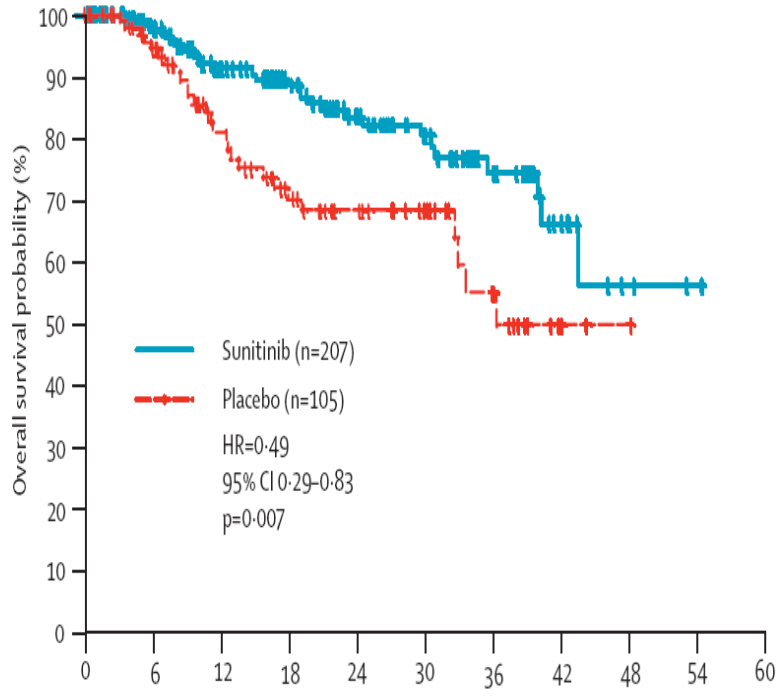
Mendel DB, et al. *Clin Cancer Res* 2003;9:327–337
Karam MW *et al. Nat Biotechnol* 2008; 26: 127–132

Sunitinib Improves PFS & OS Compared to Placebo



Number at risk

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

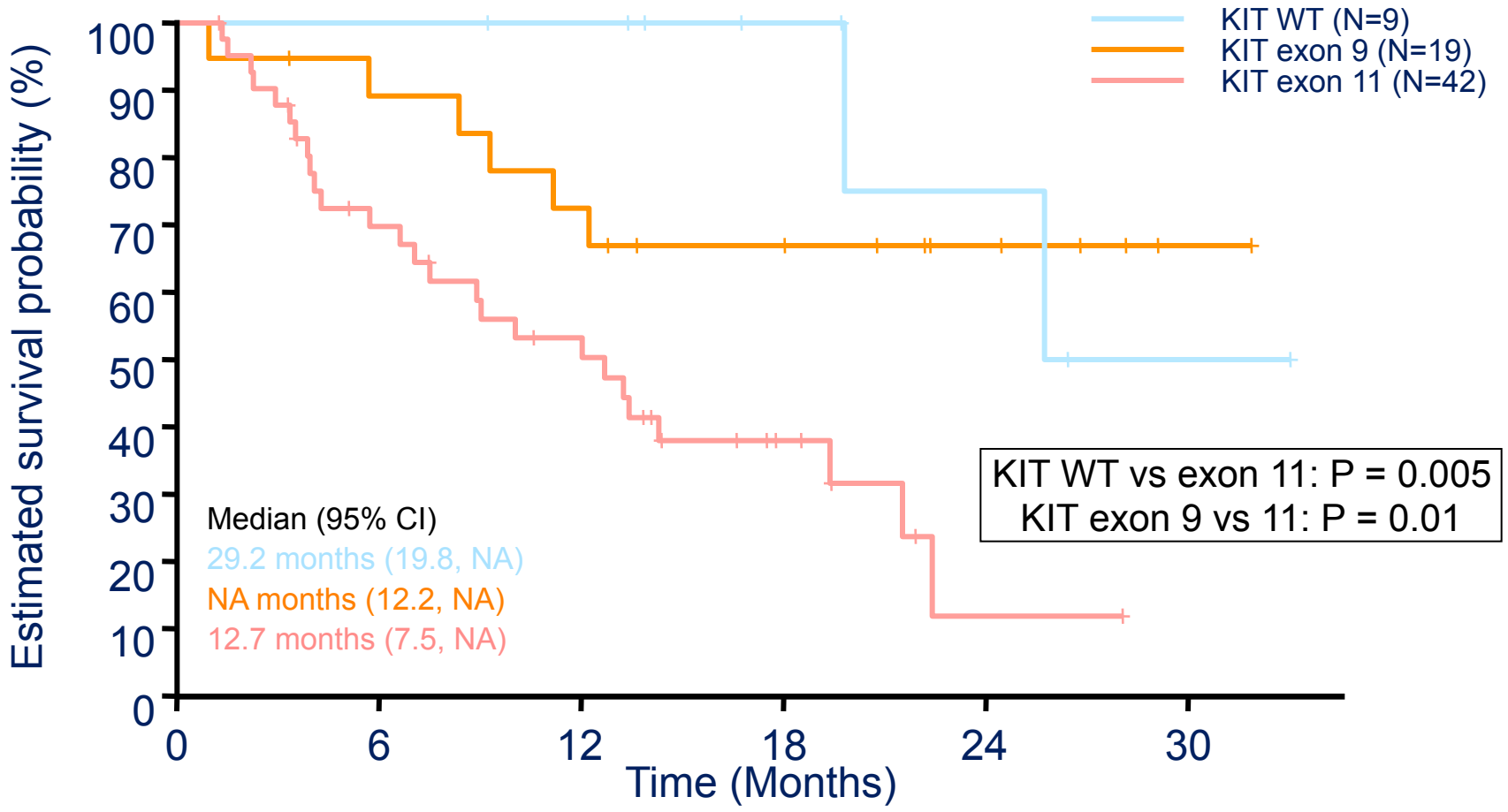


Number at risk

Sunitinib	207	167	117	97	71	50	31	11	3	1	0
Placebo	105	85	57	43	31	22	13	3	1	0	0

Demetri GD, et al. Lancet. 2006.

Sunitinib Phase I/II: OS based on 1° Mutation

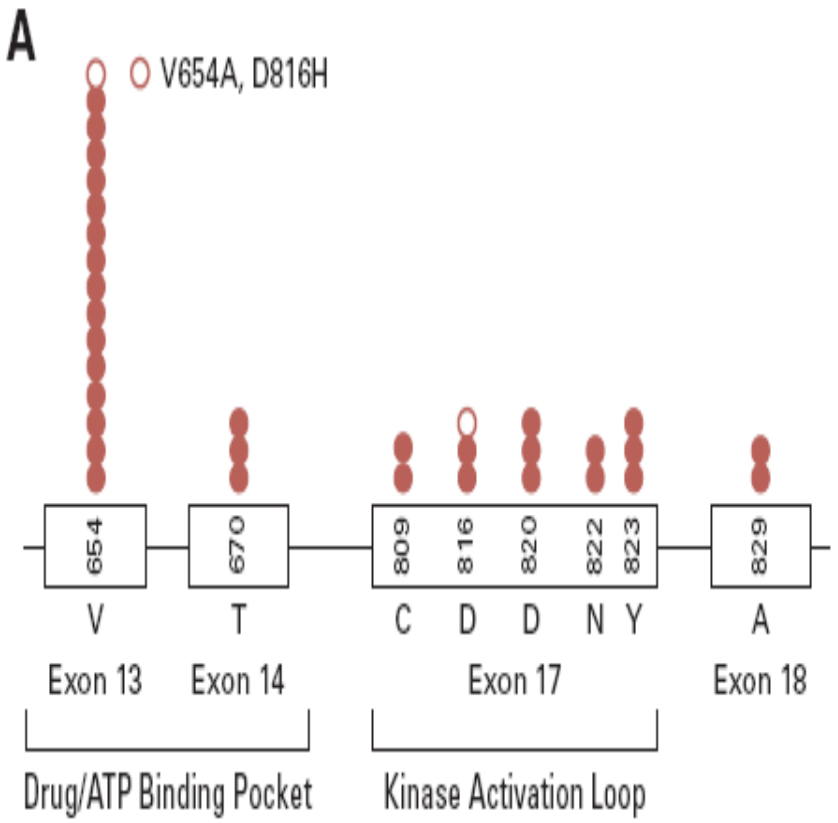


NA = not available; WT = wild type

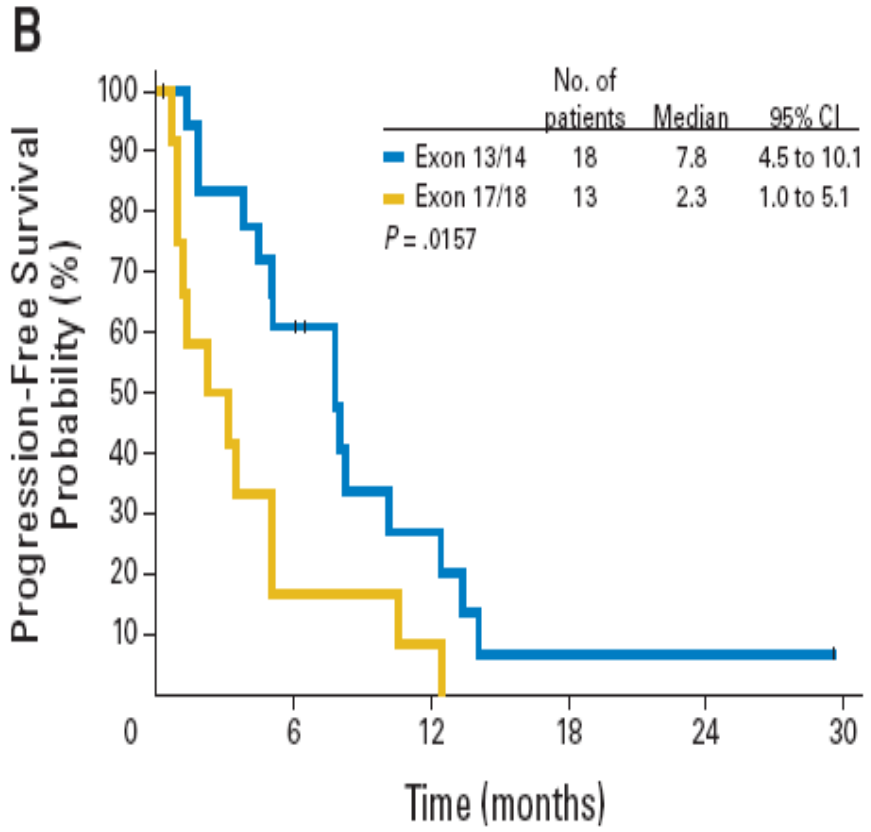
Maki R et al Proc Am Soc Clin Oncol 2005, A9011

Effect of secondary exon 11 Mutations

Site of Secondary Mutation

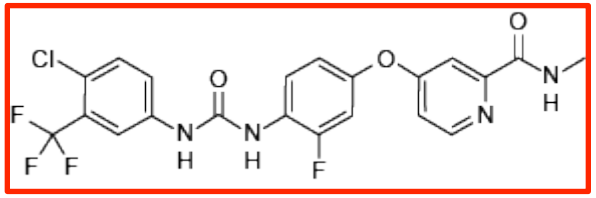


Progression Free Survival on Sunitinib

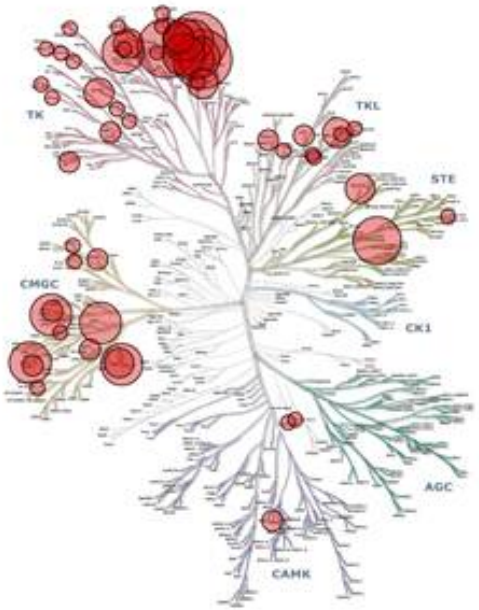


Heinrich et al. J Clin Oncol. 2006

Regorafenib (BAY 73-4506)



Regorafenib



Percent control

- 0%
- 0.1%
- 0.1-1%
- 1-5%
- 5-10%
- 10-35%

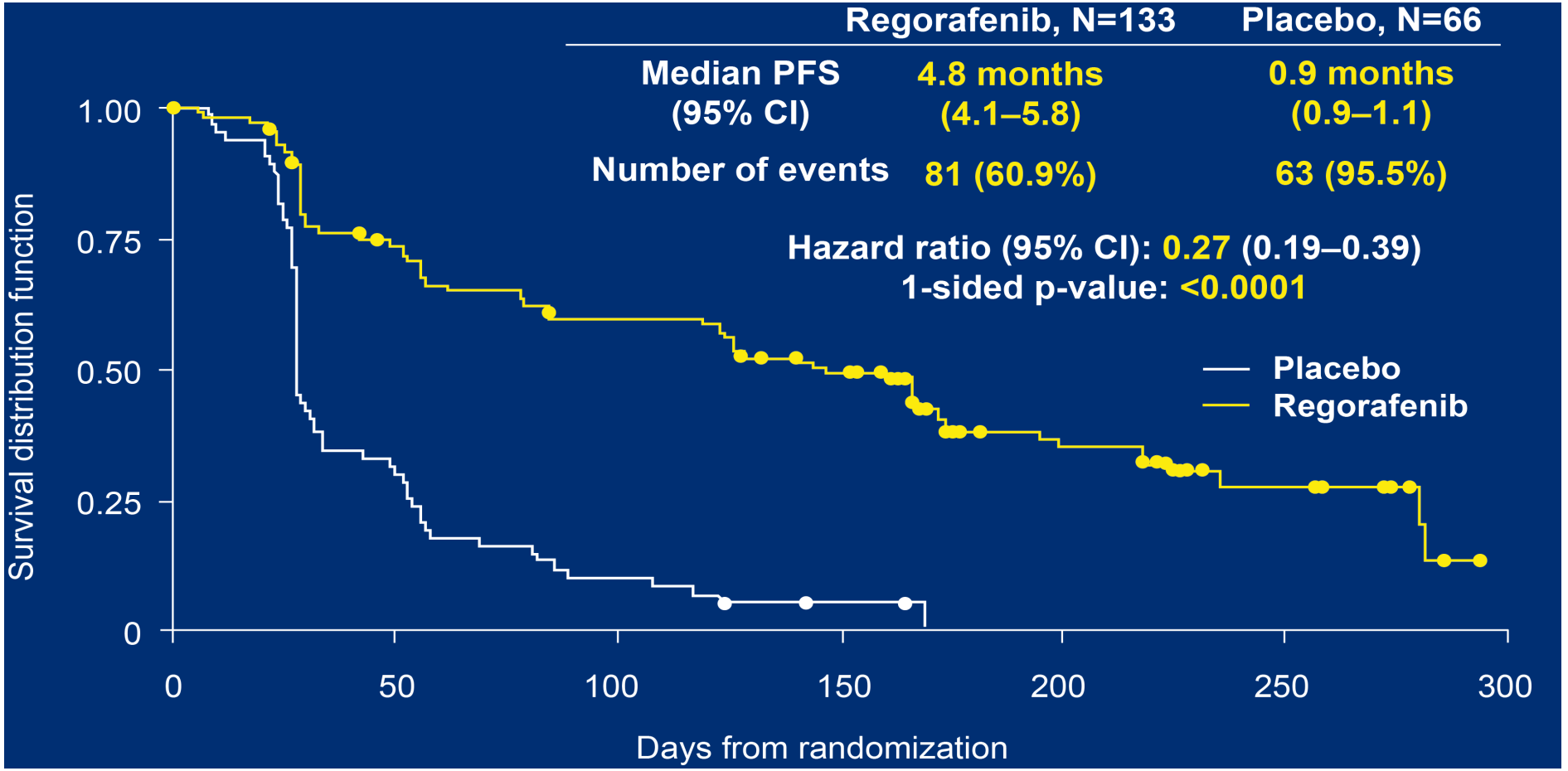
Wilhelm SM, et al. Int J Cancer 129: 245-25, 2011

Biochemical activity

	IC_{50} (nmol/l)
KIT	7
VEGFR-1	13
Murine VEGFR-2	4
PDGFR-β	22
RET	1.5
B-RAF	28
FGFR1	202

Demetri et al. ASCO 2012

GRID Study: Progression-Free Survival



Regorafenib significantly improved PFS *vs* placebo (p<0.0001); primary endpoint met

Demetri et al. ASCO 2012

Benefit of Regorafenib based upon Primary Mutation

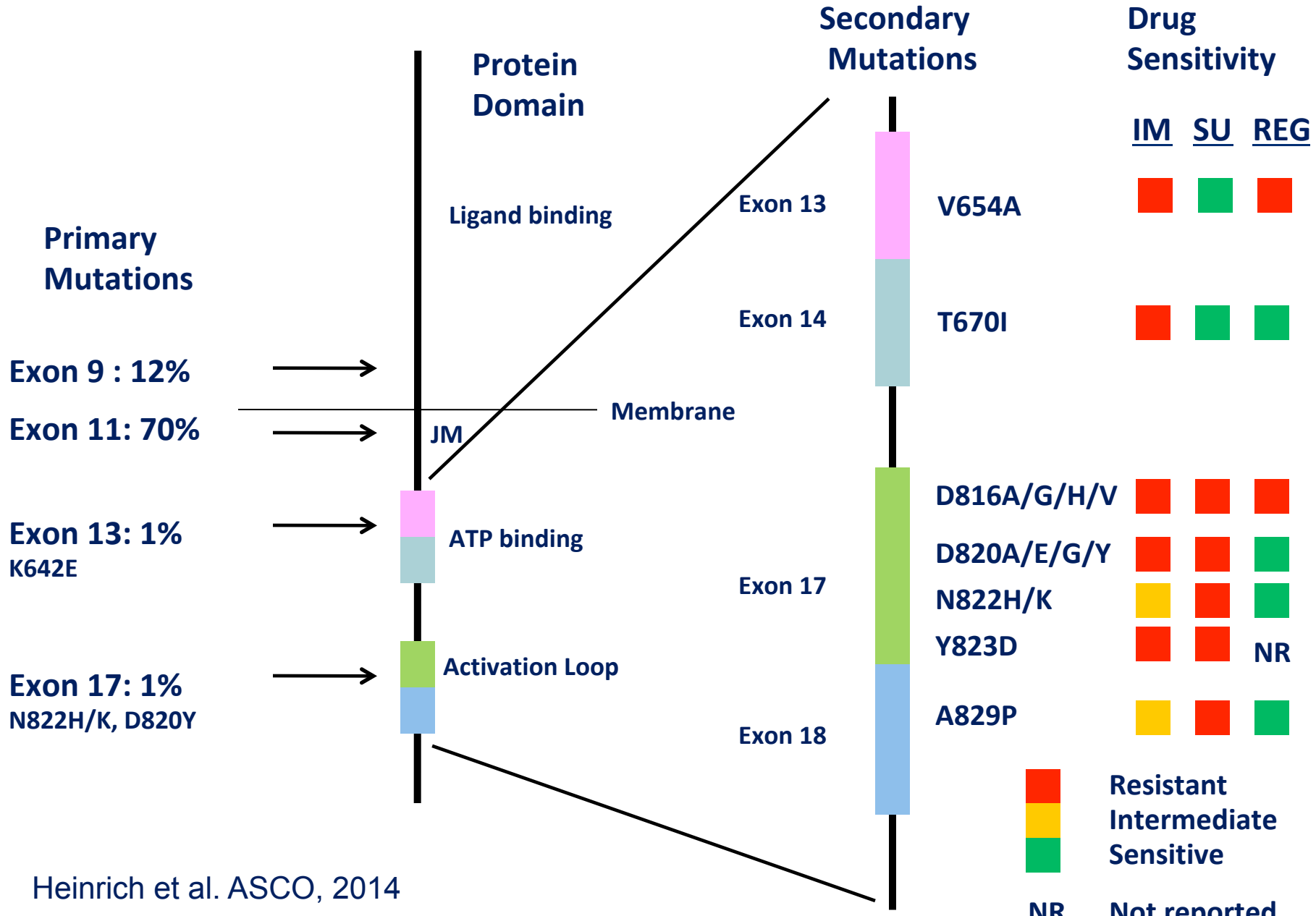
Progression-free survival (PFS)

Mutation status	Placebo (N=15) median months	Regorafenib (N=51) median months
KIT exon 11 mutation	1.1	**5.6**
KIT exon 9 mutation	0.9	**5.4**

Phase II study of Regorafenib	Response %		PFS (median months)
SDH-deficient tumors (N=6)	PR: 33.3	SD: 66.7	10

Demetri et al. ASCO 2012
Ben-Ami et al. Annals of Oncology 2016

KIT Mutation Site and Drug Sensitivity



Heinrich et al. ASCO, 2014

Summary

Primary resistance

1L imatinib — ORR ~60%, PFS 19 mo

2L sunitinib — ORR ~7%, PFS 6 mo

Secondary resistance

3L regorafenib — ORR ~5%, PFS 4.8 mo

4L no approved therapy — ORR ~0%, PFS ≤1.8 mo*

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

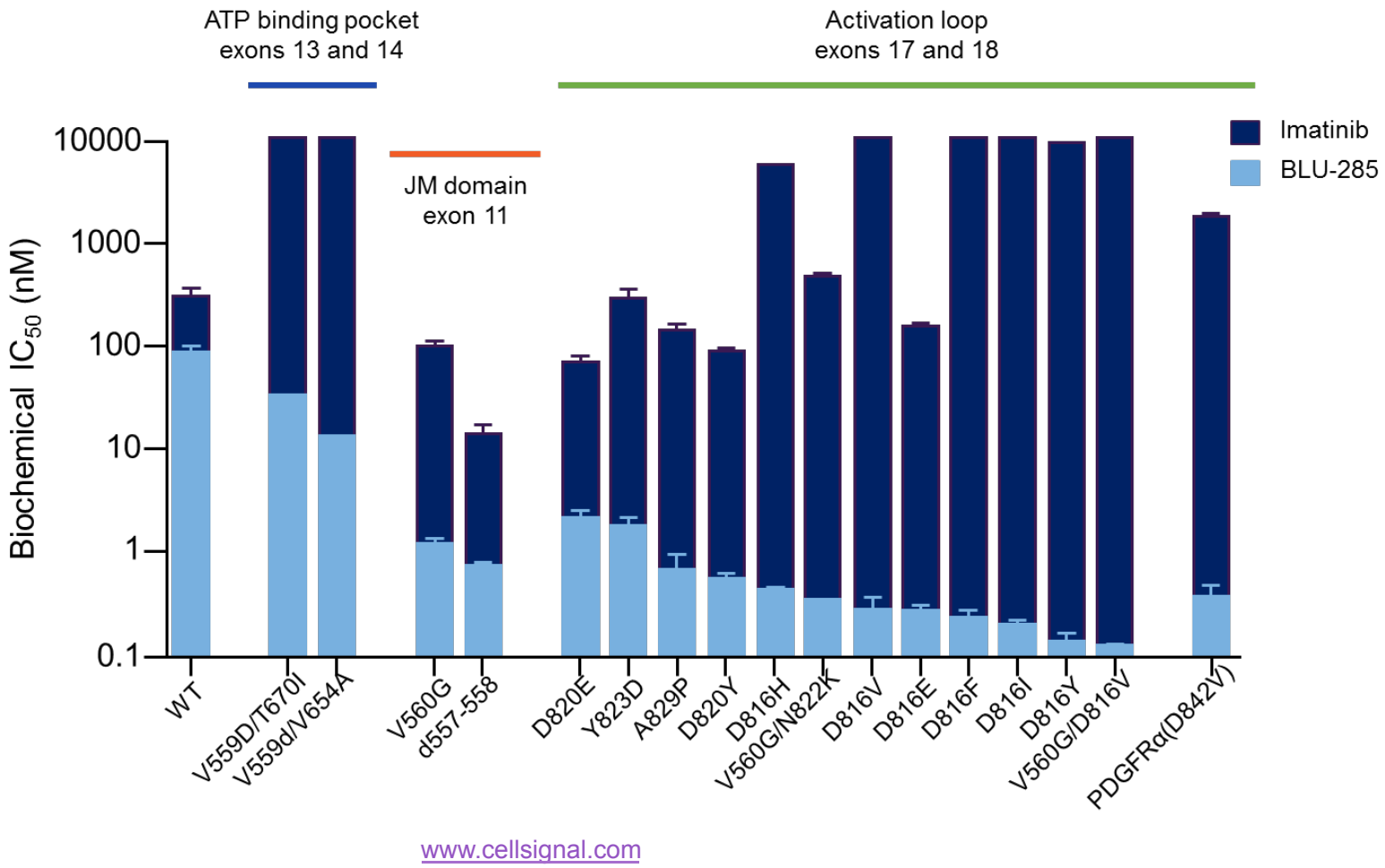
Primary and secondary mutations cause therapeutic resistance

Approved agents are ineffective against PDGFRα D842V

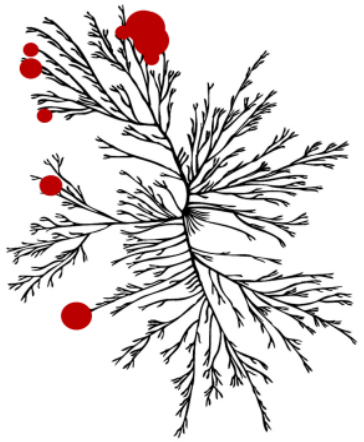
Heinrich MC et al. ASCO 2017

NEW APPROACHES

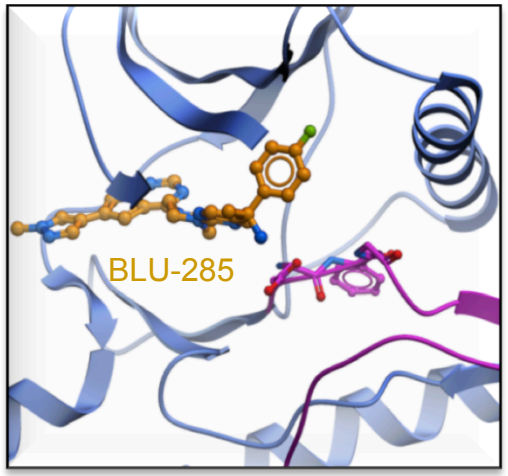
Avapritinib (BLU-285): potent against KIT/PDGFRα GIST mutants



www.cellsignal.com



- High kinome selectivity



- Binds active conformation

Heinrich MC et al. ASCO 2017

BLU-285 Phase 1 study

Key objectives

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

Advanced GIST → MTD

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

PDGFRα D842V-mutant GIST (n=50)

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

- Starting dose: 300 mg daily
- If treatment tolerated for 2 cycles, dose escalation to 400 mg daily allowed at the discretion of the treating MD

Heinrich MC et al. ASCO 2017

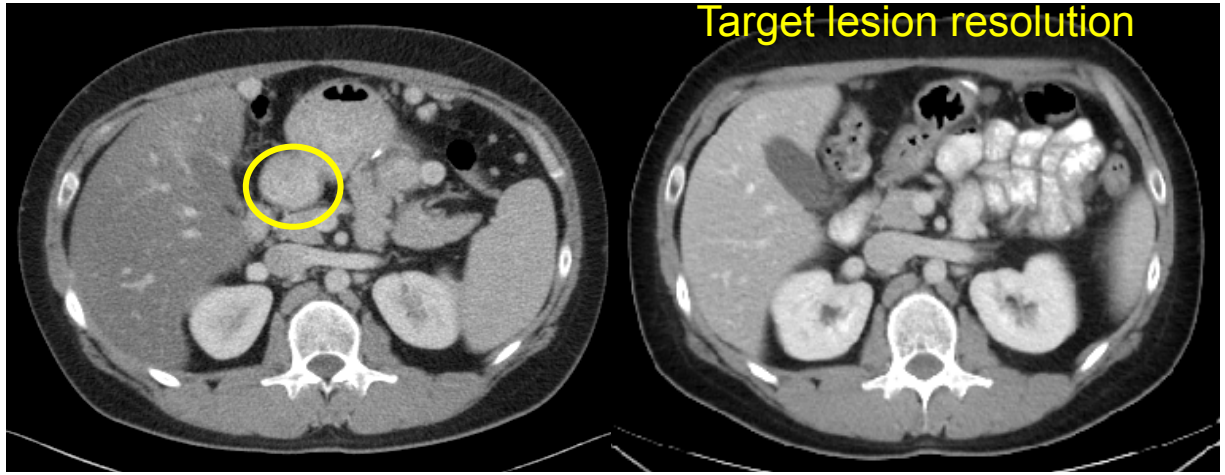
Baseline patient characteristics

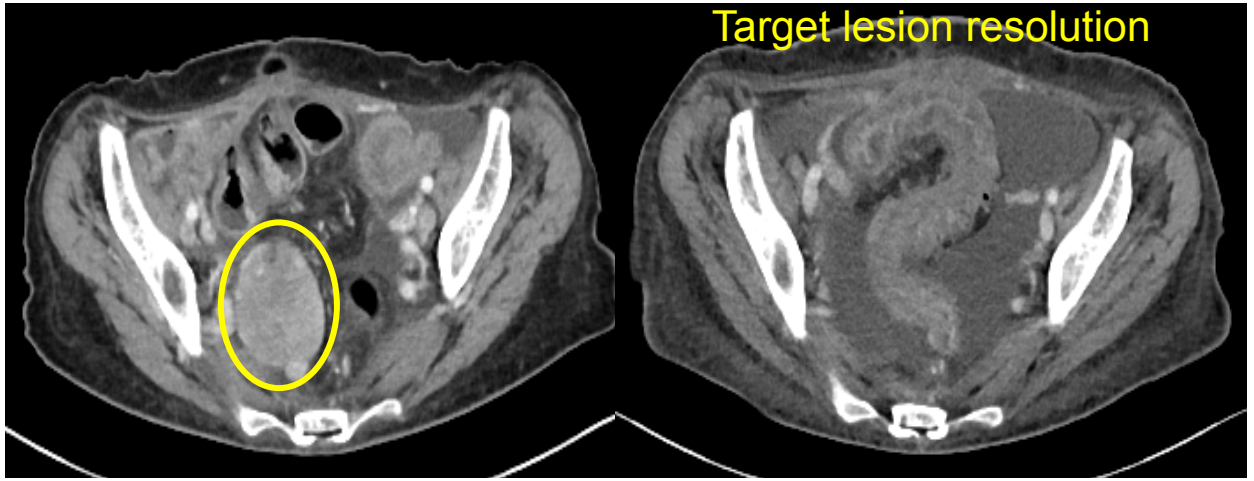
Parameter	All patients, N=72	
Age (years), median (range)	61 (25–85)	
	n (%)	
GIST subtype		
KIT mutant	40 (56)	
PDGFRα mutant	32 (44)	
Metastatic disease	69 (96)	
Largest target lesion size (cm)		
≤5	18 (25)	
>5–≤10	25 (35)	
>10	29 (40)	
No. prior kinase inhibitors	PDGFRα	KIT
Median (range)	1.5 (0–6)	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

Heinrich MC et al. ASCO 2017

Response in PDGFRα D842V-mutant GIST



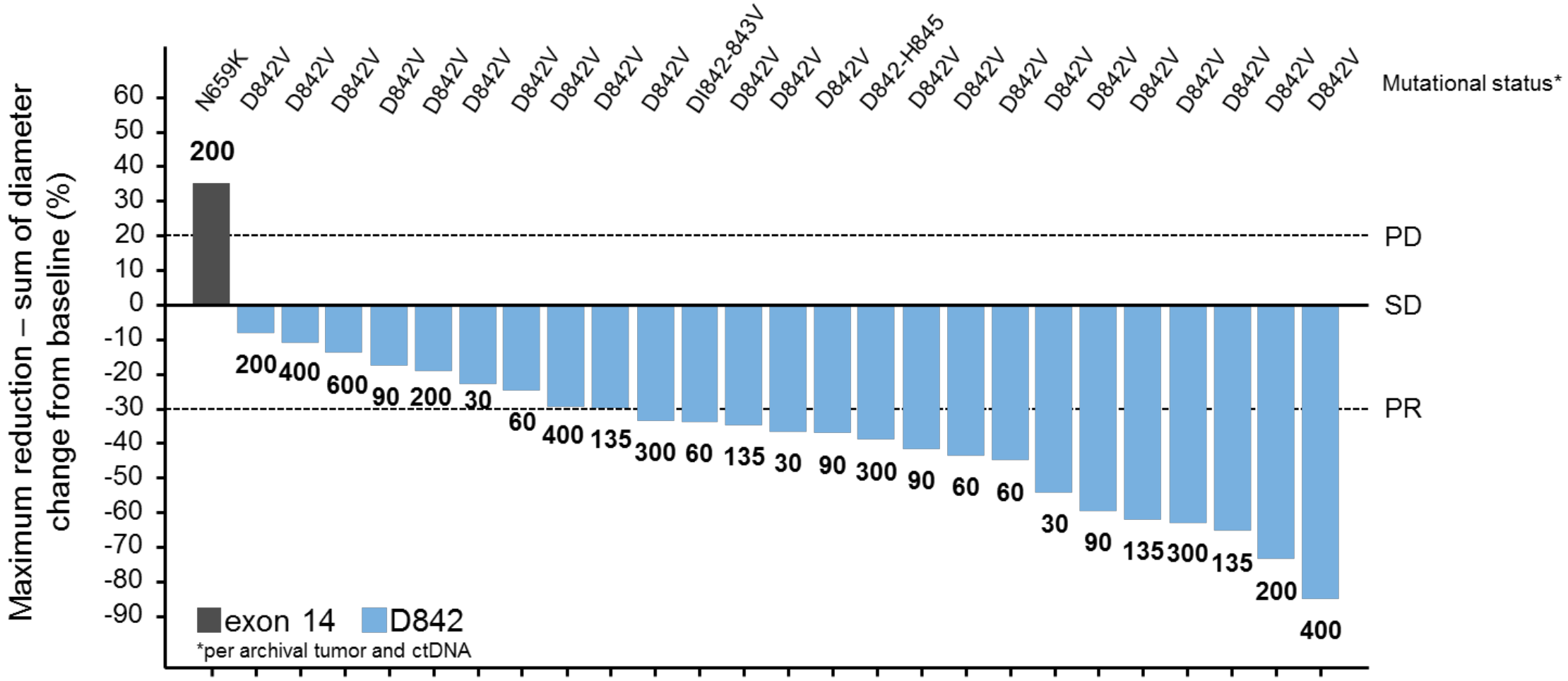


- Ongoing at cycle 5
- Prior imatinib and sunitinib
- Partial response, size decreased by 63%

- Ongoing at cycle 3
- Prior imatinib
- Partial response, size decreased by 85%

Heinrich MC et al. ASCO 2017

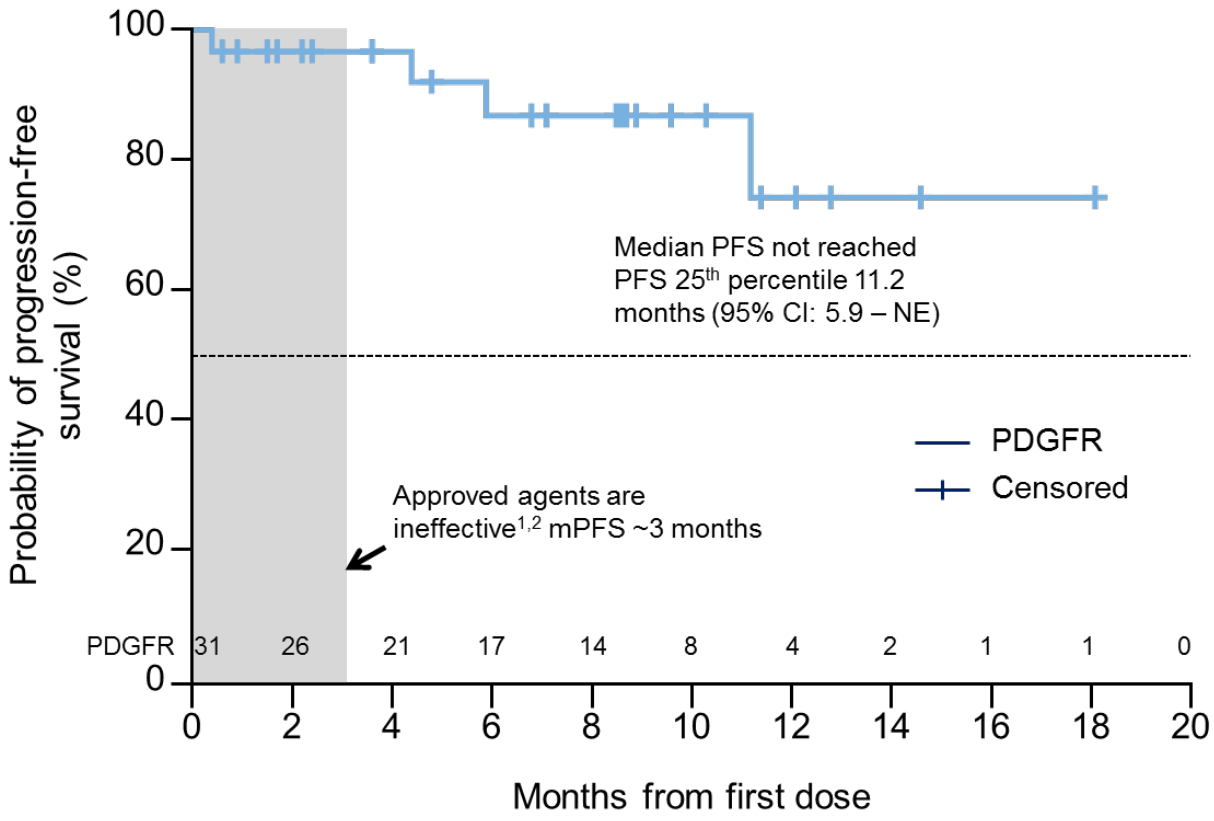
Tumor regression across all dose levels in PDGFRα D842-mutant GIST



Heinrich MC et al. ASCO 2017

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

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

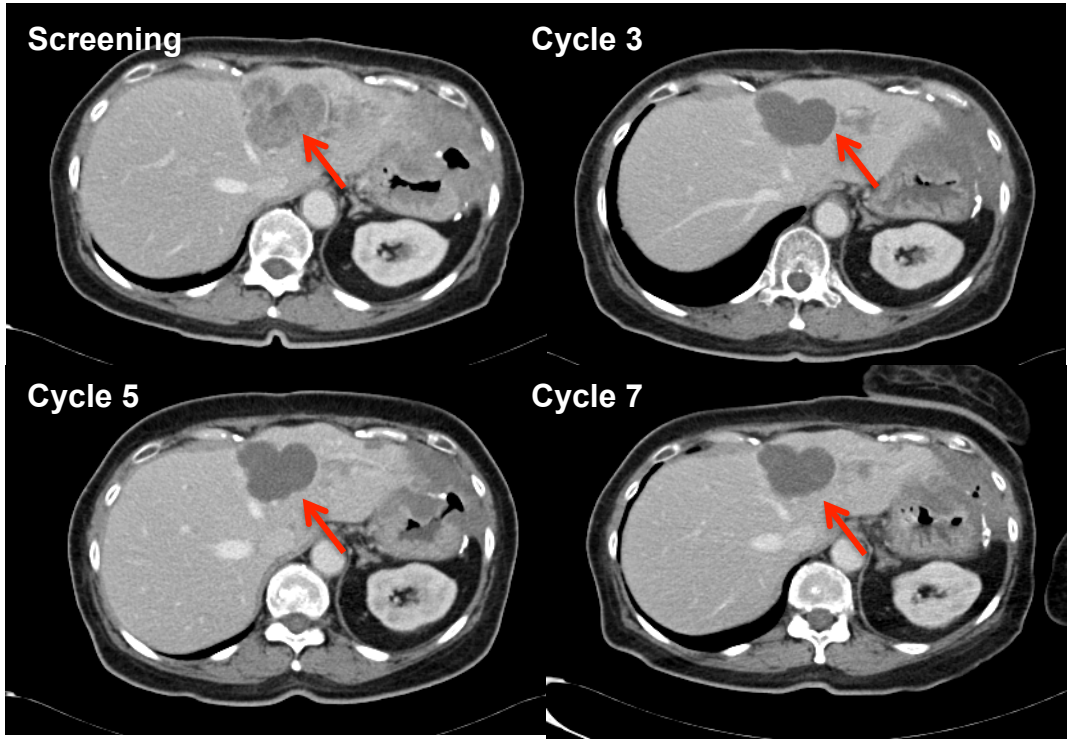


Approved agents are ineffective: ORR ~0%

Heinrich MC et al. ASCO 2017

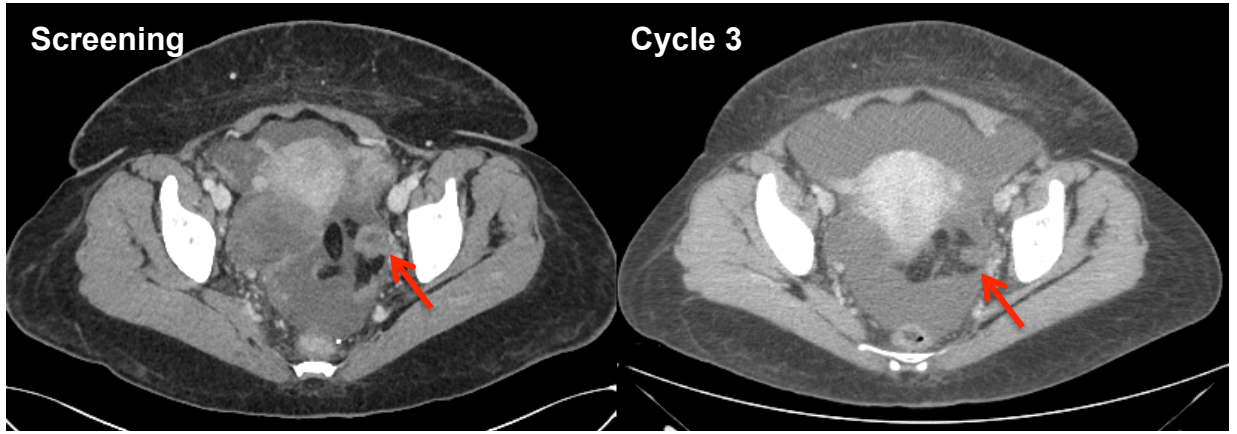
Radiographic response in heavily pre-treated KIT-mutant GIST

BLU-285 300 mg (dose escalation)



- Ongoing at cycle 12
- 6 prior TKIs; exon 11, 13, and 18 mutations
- CHOI

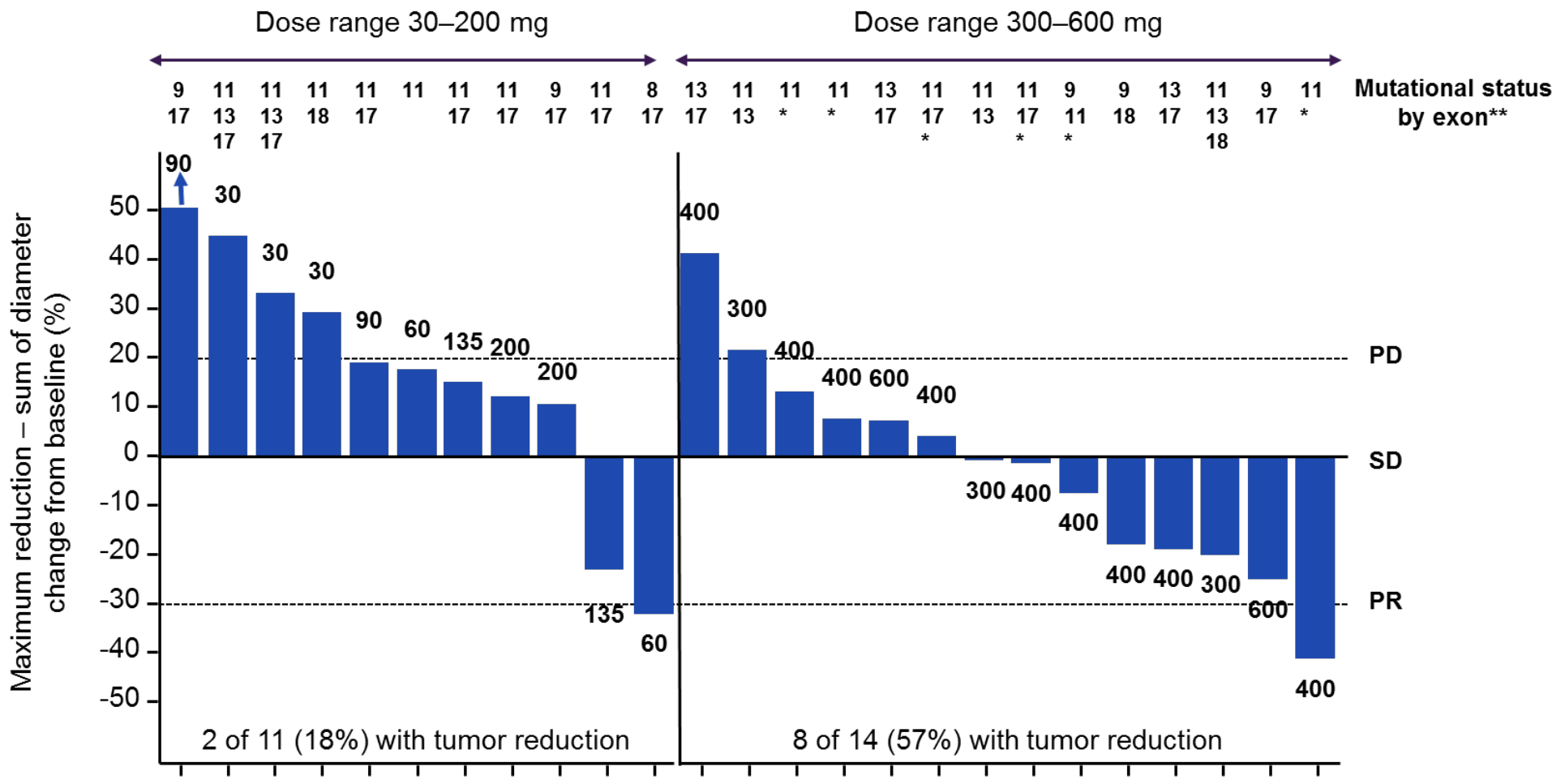
BLU-285 400 mg (dose expansion)



- Ongoing at cycle 4
- 5 prior TKIs; 1° exon 11 mutation; ctDNA pending
- CHOI

Heinrich MC et al. ASCO 2017

Dose-dependent tumor reduction across multiple KIT genotypes



*ctDNA results pending

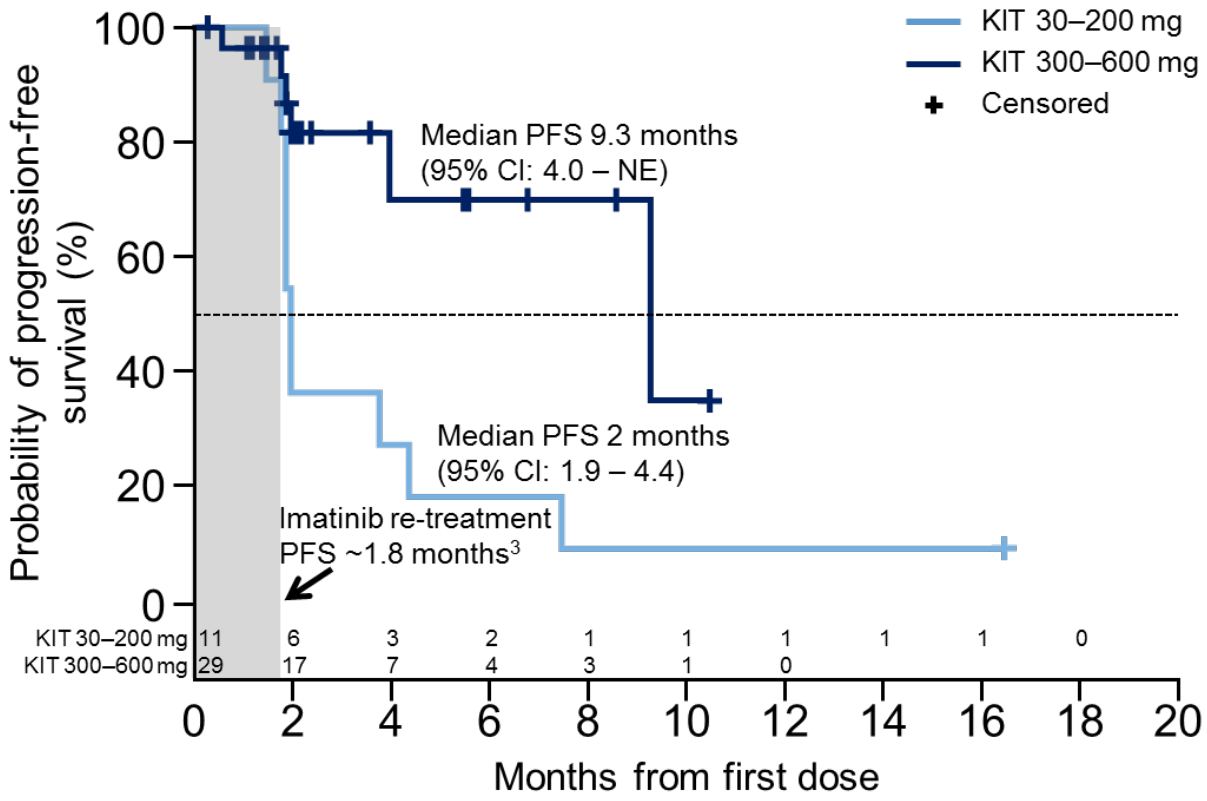
**per archival tumor and ctDNA

Important clinical activity in heavily pre-treated KIT-mutant GIST

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)

Beyond third-line regorafenib there are no approved therapies

- Imatinib re-treatment in ≥third-line GIST[3]
  - ORR ~0%



Heinrich MC et al. ASCO 2017

Adverse events (AE) associated with BLU-285

Safety population, N=72	
AEs in ≥20% of patients	**n (%)**
Nausea	**43 (60)**
Fatigue	**38 (53)**
Vomiting	**30 (42)**
Periorbital edema	**26 (36)**
Diarrhea	**24 (33)**
Edema peripheral	**22 (31)**
Decreased appetite	**20 (28)**
Anemia	**18 (25)**
Lacrimation increased	**17 (24)**
Dizziness	**16 (22)**

Sever toxicities thought to be 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

Cognitive effects: includes issues with concentration, memory, mood changes

Recommendations for dose interruption and consideration of dose reduction

Heinrich MC et al. ASCO 2017
Heinrich MC et al. CTOS 2018

Voyager: Study of Avapritinib vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic GIST

- Randomized
- open label
- 1:1 ration

Avapritinib 300 mg daily continuously

Regorafenib 160 mg daily 3 weeks on, 1 week off

PROGRESSION

Continued Avapritinib 300 mg daily or discontinuation

Avapritinib 300 mg daily continuously

- Previoulsy treated with imatinib and 1 or 2 other TKI's
- Documented KIT/ PDGFRA mutation

Study endpoints: PFS based on independent radiology assessment
Secondary endpoints: Response rate, Overall Survival, Quality of Life, Time to tumor progression, Safety profile.

Current Status

- Blueprint filed a New Drug Application on 6/14/19 with U.S. Food and Drug Administration for avapritinib for the treatment of adult patients with **PDGFRA Exon 18 mutant gastrointestinal stromal tumors (GIST), regardless of prior therapy, and fourth-line GIST.**

Current Status

- Plans for trial in the second line setting compared with sunitinib
- Also establishing a compassionate use program at a variety of centers nation wide.

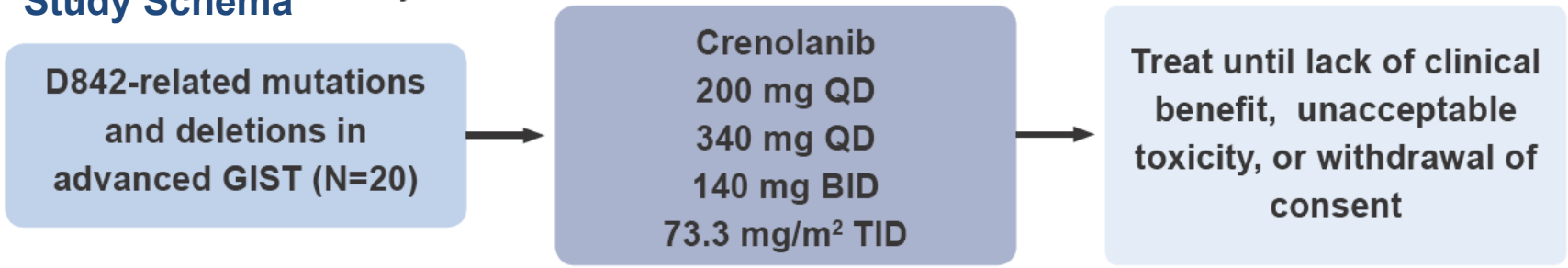
ARO-002: Crenolanib in D842V GIST

Study Design

ARO-002 was a dose-escalating study with 4 dosing cohorts to assess clinical benefit of crenolanib in patients with advanced GIST with *PDGFRA* D842V activating mutations.

Primary Objectives	Secondary Objectives
Response Rate	PFS
	Safety
	Pharmacokinetics

Study Schema



von Mehren et al., Proc. ASCO: 2016. abstract 11010

31% Overall Clinical Benefit

5/16 (31%) of patients with D842V mutated GIST derived clinical benefit from crenolanib treatment.

- 2 (13%) patients achieved a partial response.
- 3 (19%) patients achieved stable disease.

Overall Response Rate

Evaluable Patients (N=16*)		
Response	# of Patients	Percentage (%)
PR	2	13%
Stable Disease	3	19%
Overall clinical benefit (CR+PR+SD)	5	31%

*Non-evaluable patients included:

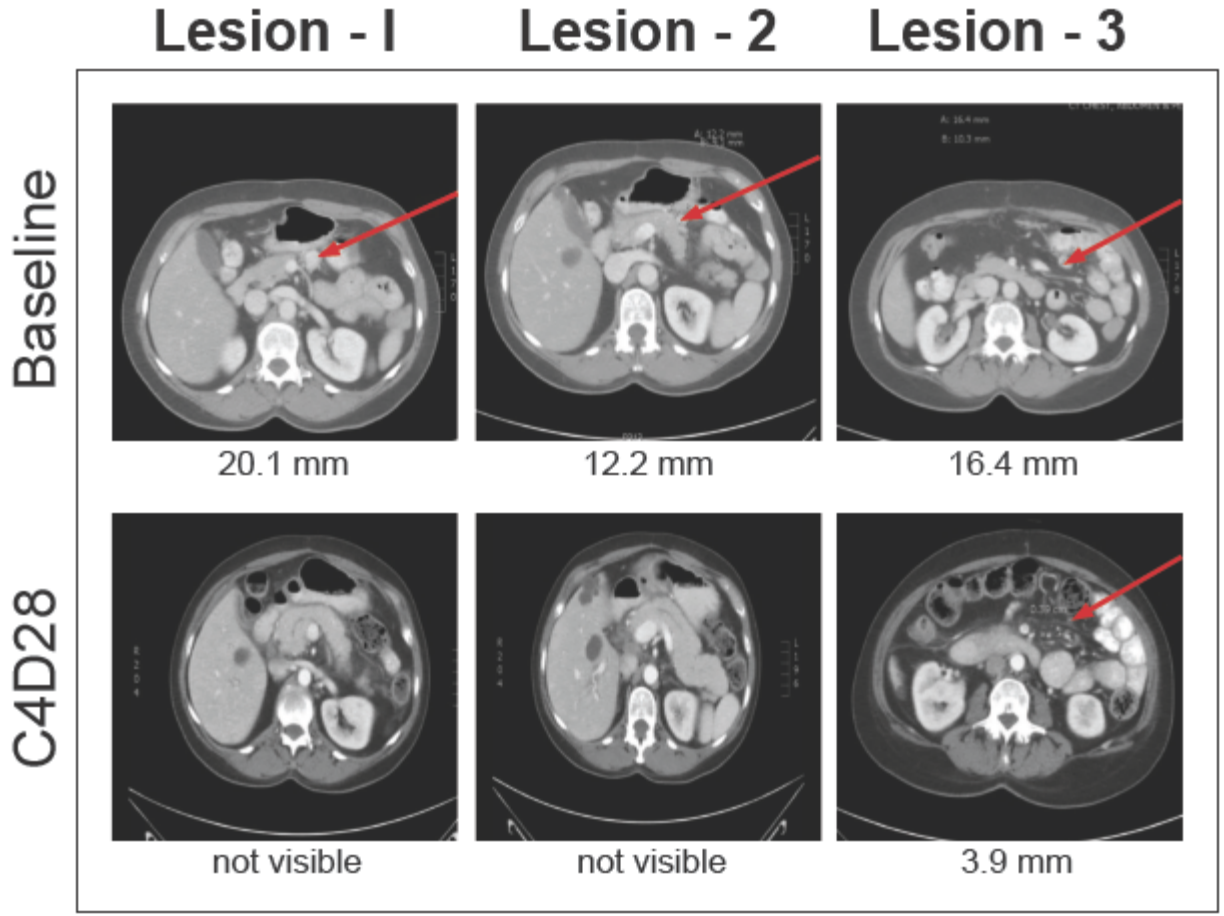
- 3 patients off study prior to receiving 1 full cycle and
- 1 did not have recurrent GIST (aggressive fibromatosis).

von Mehren et al., Proc. ASCO: 2016. abstract 11010

PR after 4 cycles of Crenolanib

Patient case: 62 year old female

- Patient achieved a partial remission at 140 mg BID



von Mehren et al., Proc. ASCO: 2016. abstract 11010

Current Status

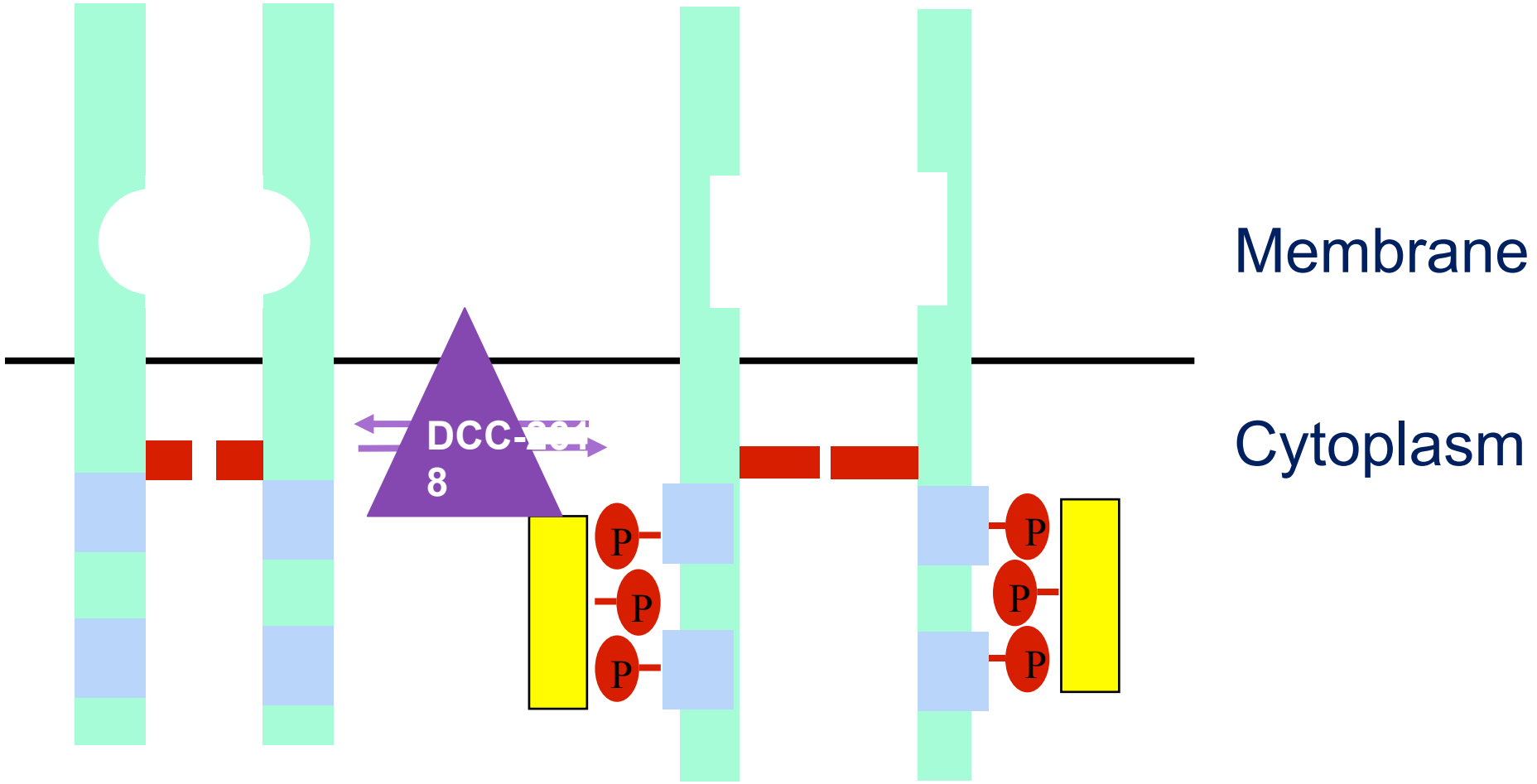
- A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Trial of Crenolanib in Subjects with Advanced or Metastatic Gastrointestinal Stromal Tumors with a D842V Mutation in the PDGFRA Gene

Repretinib (DCC-2618) background

- Novel mechanism of action
- Preclinical broad range activity against GIST relevant KIT and PDGFRA primary and secondary mutations
- Also has activity against FLT-3, PDGFRB, KDR, TIE2 and FMS

Repretinib (DCC2618): Mechanism of Action

Type II switch control kinase inhibitor of KIT and PDGFRα



DCC-2618 – Phase 1 Study Design and Methods

Part 1: Dose Escalation

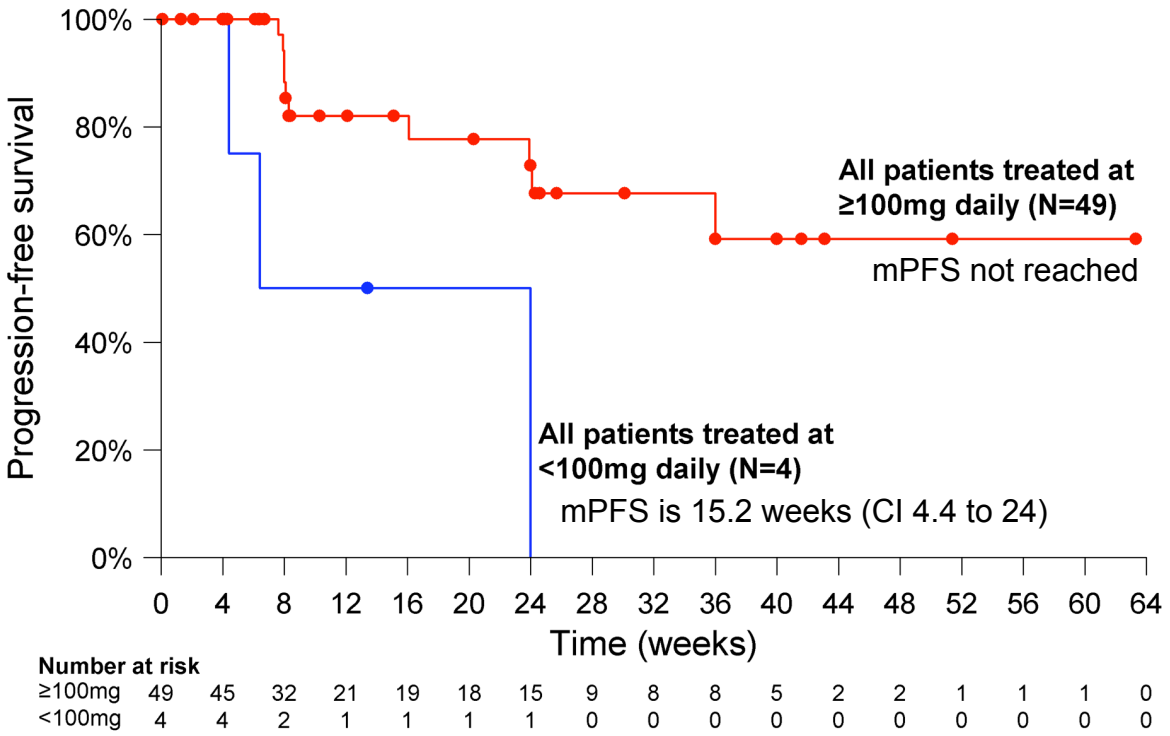
- Key Objectives: MTD, recommended Phase 2 dose (RP2D), safety, tolerability, pharmacokinetics and anti-tumor activity (NCT# 02571036)
- Design: 3+3 design for Patients with advanced refractory cancers (KIT/PDGFRα mutated) with a focus on GIST
- Dose Levels tested: 20, 30, 50, 100, 150, and 200 mg BID; and 100, 150 and 250 mg QD - IPDE(1) to 150mg BID permitted
- CT scans every 2 cycles
- ECOG 0-2; adequate end organ function
- MTD: not determined

Part 2: Dose Expansion @ 150 mg QD (RP2D)

- Various cohorts :
  - 3 GIST by line of therapy (2^{nd}-3^{rd}, 4^{th}, > 4^{th} line)
- Dose escalation n to 150mg BID permitted at RECIST progression

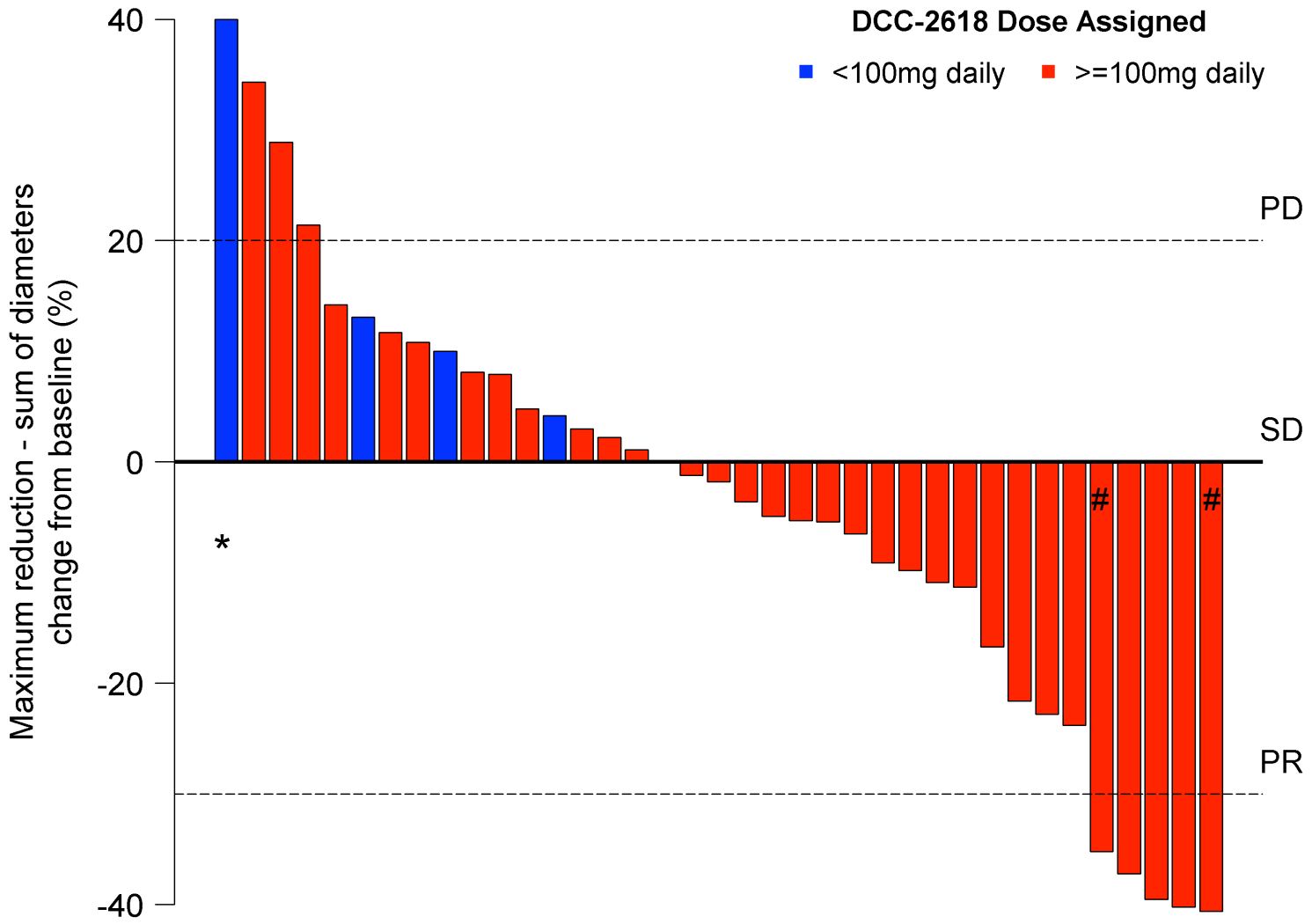
DCC-2618: PFS for doses ≥100 mg/d compared to <100 mg/d

- 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 (NCT02571036)



Janku et al. ESMO, 2017

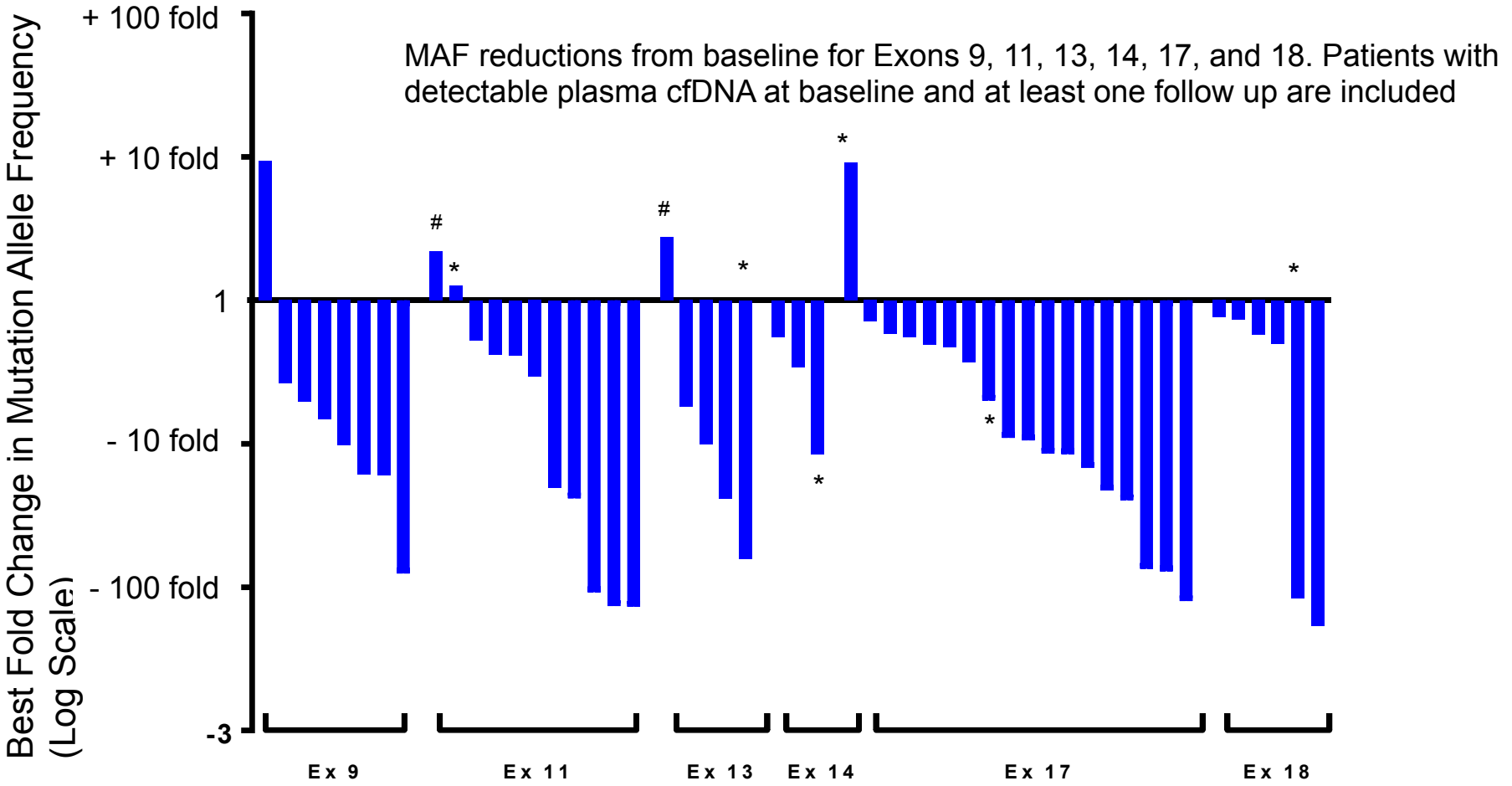
Waterfall Plot of KIT/PDGFRA GIST Patients, N=37



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

Janku et al. ESMO, 2017

cfDNA Pharmacodynamic Biomarker Demonstrates pan−KIT Activity (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

Janku et al. ESMO, 2017

Baseline Characteristics GIST Patients at ≥100 mg/d DCC-2618 (n=178)

	2nd Line (n=38)	3rd Line (n=29)	≥ 4th Line (n=111)[4]	Total (n=178)
Age Median (min, max)	60 (32, 80)	64 (48, 82)	60 (27, 87)	61 (27, 87)
ECOG PS 0-1	38 (100%)	29 (100%)	108 (97%)	175 (98%)
ECOG PS 2	0 (0%)	0 (0%)	3 (3%)	3 (2%)
Primary Mutation[1] n (%)				
KIT Exon 9	4 (11%)	8 (28%)	22 (20%)	34 (19%)
KIT Exon 11	31 (82%)	20 (69%)	71 (64%)	122 (69%)
Other KIT[2]	0 (0%)	1 (3%)	12 (11%)[3]	13 (7%)[3]
PDGFRα	3 (8%)	0 (%)	6 (5%)	9 (5%)
Pts at RP2D (150 mg QD)	32 (84%)	27 (93%)	83 (75%)	142 (80%)

Notes: (1) Primary mutation per local assessment; (2) KIT exon 13 (4), KIT exon 17 (5), not done (3); (3) Includes one SDH deficient patient; (4) Mean # is 4.63 (range 4- 7).

DCC-2618 has Encouraging Efficacy across all Lines at ≥100 mg/d

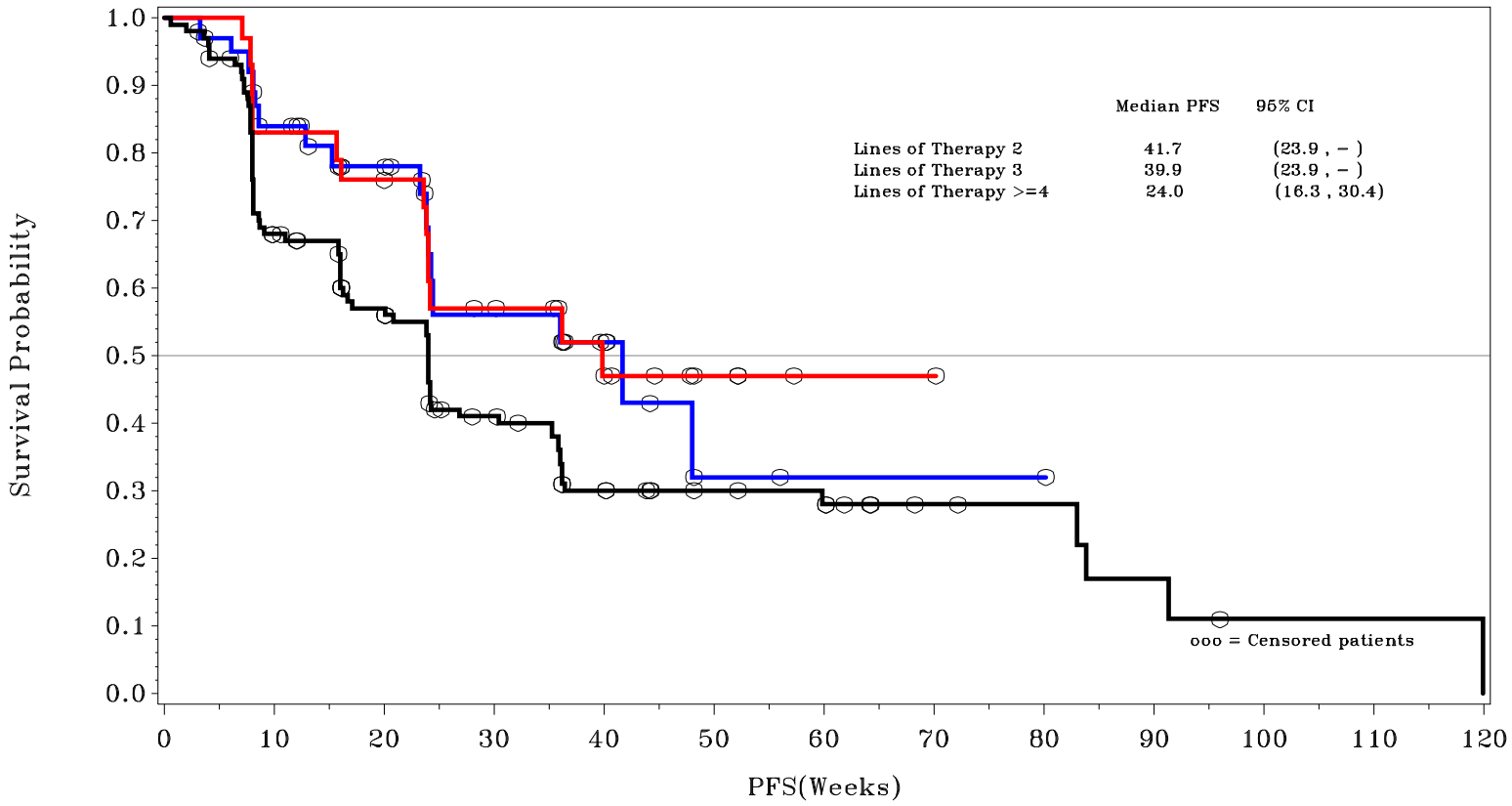
Line of Therapy	Objective Response Rate[1]	Disease Control Rate @ 3 Months	Median Progression Free Survival (mPFS)	Censored Patients for mPFS	Median Treatment Duration[4]
2nd Line (n=38)	18%[2] (7/38)	79%	42 weeks (24, NE)	58%	48 weeks (31, NE)
3rd Line (n=29)	24% (7/29)	83%	40 weeks (24, NE)	52%	NR (36, NE)
≥4th Line (n=111)	9% (10/106)[3]	66%	24 weeks (16, 30)	35%	28 weeks (22, 47)
2nd & 3rd Line (n=67)	21%[2] (14/67)	81%	40 weeks (24, NE)	55%	52 weeks (36, NE)

Notes: (1) Includes 9 unconfirmed responses in 2nd line (n=1), 3rd line (n=3) and ≥4th line (n=5); (2) Does not reflect 1 PR reported after cut off date; (3) Excludes 5 patients due to due to missing data at the time of data cut off (n=2), lack of first tumor assessment (n=1), withdrawal of consent prior to first assessment (n=1) and unrelated death at C1D4 prior to first assessment (n=1); (4) Includes 46 patients who elected for intra-patient dose escalation.

mPFS by Line of Therapy for ≥100 mg/d DCC-2618 (n=178)

Lines	N	mPFS	Number Censored	Active Patients
2	38	42 weeks	22 (58%)	61%
3	29	40 weeks	15 (52%)	59%
4+	111	24 weeks	40 (36%)	44%

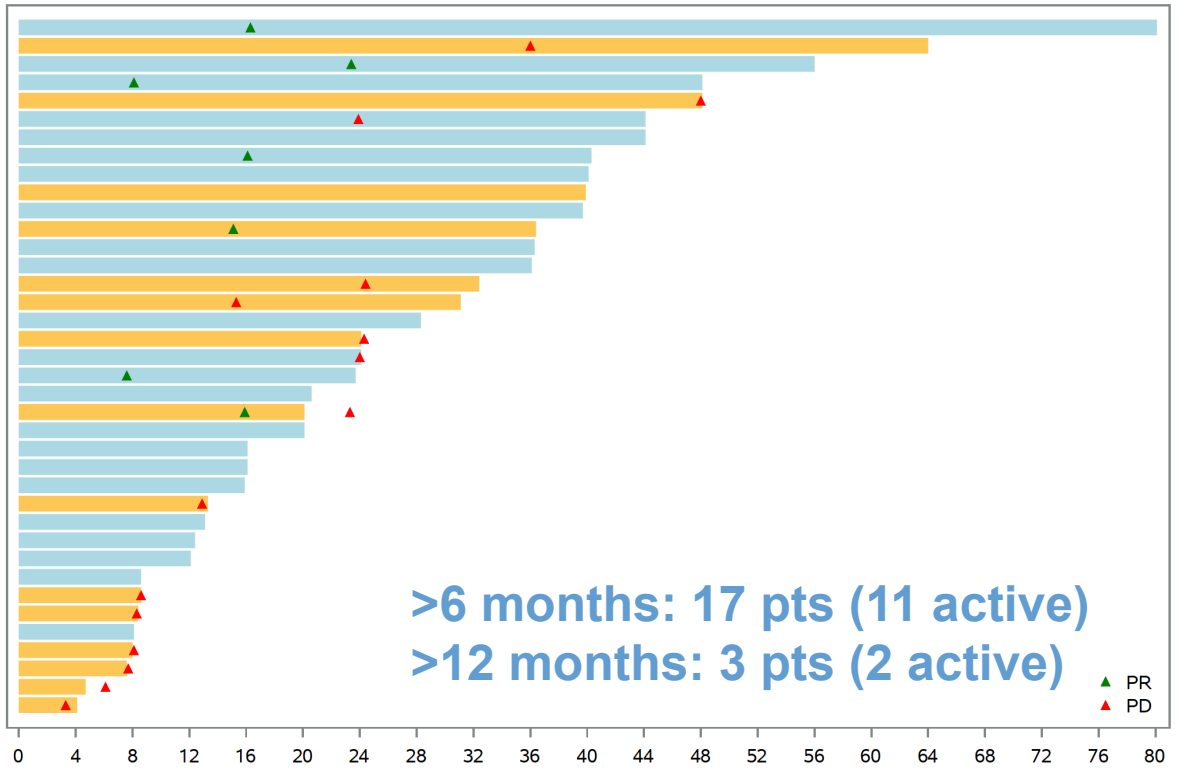
- DCC-2618 demonstrated prolonged progression free survival in a meaningful subset of patients across all lines of treatment
- Following progression, 63% (n=29) and 28% (n=13) of patients stayed on study for >8 and >16 weeks, respectively



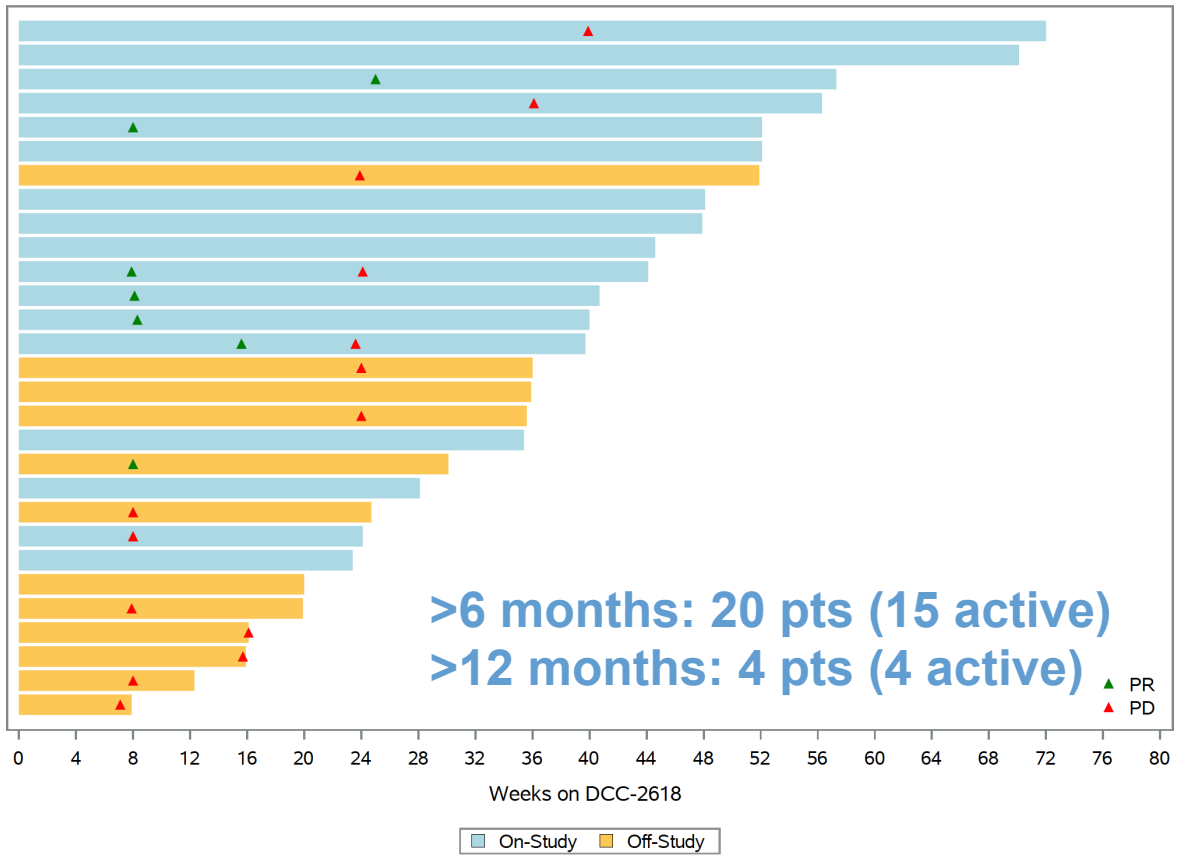
2nd Line	38	30	21	13	8	2	1	1	1	0	0	0	0
3rd Line	29	24	21	14	8	4	1	1	0	0	0	0	0
≥4th Line	111	71	53	32	20	14	12	6	5	3	1	1	0

Good Tolerability Allowed for Prolonged Treatment

2nd Line Patients (n=38)

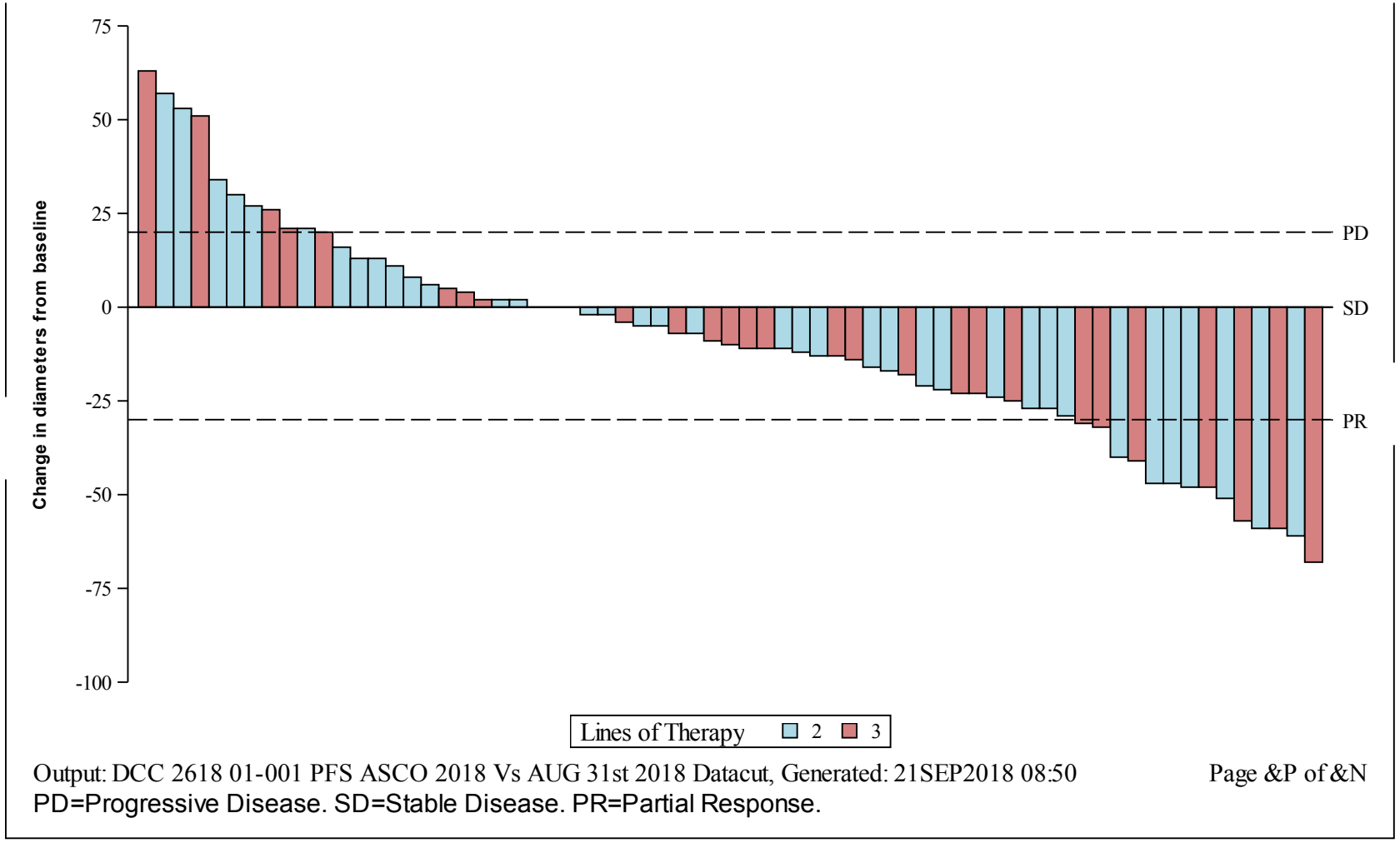


3rd Line Patients (n=29)



Notes: (1) Includes 4 unconfirmed responses in 2nd line (n=1) and 3rd line (n=3); (2) Does not reflect 1 PR after cut off date; (3) Includes 14 patients who elected for intra-patient dose escalation.

Best Response by RECIST in 2nd & 3rd Line GIST Patients at ≥100 mg/d DCC-2618 (n=67)



2nd Line (n=38)

- 7/38 PRs(1) (18%) as of data cut off

3rd line (n=29)

- 7/29 PRs(1) (24%) as of data cut off

2nd & 3rd line (n=67)

- 14/67 PRs (1) (21%) as of data cut off

Notes: (1) Includes unconfirmed responses in 2nd line (n=1) and 3rd line (n=3).

DCC-2618 – TEAE in >10 % of GIST Patients at ≥100 mg/d

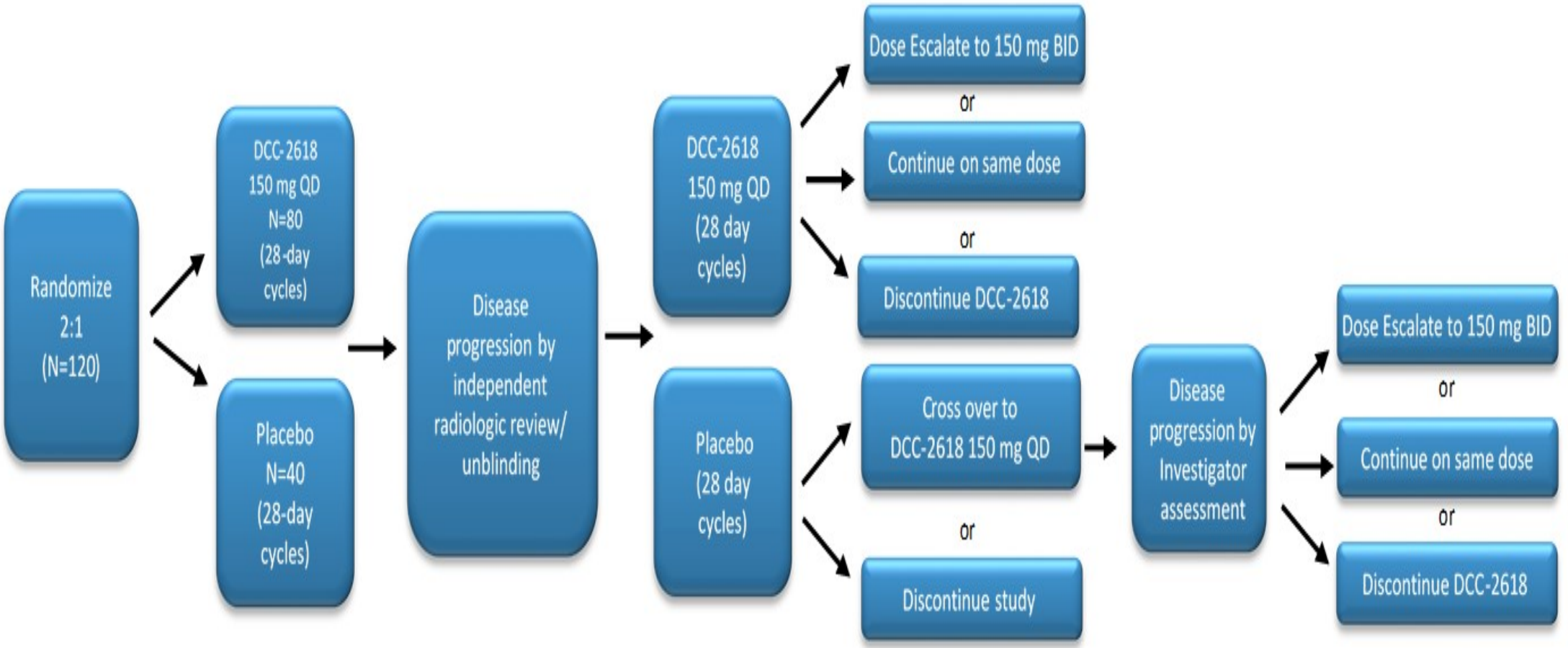
Out of 178 patients treated with DCC-2618 at ≥100 mg/d

- 24 (14%) experienced dose reductions due to TEAE
- 19 (11%) experienced treatment discontinuations due to TEAE
- Clinically asymptomatic lipase elevations most frequent G3 TEAE

Notes: (1) Treatment Emergent Adverse Events; (2) Palmar-plantar erythrodysaesthesia syndrome was reported in 19 patients.

Preferred Term	Grade 1-2 (n=178)	Grade 3-4 (n=178)	Grade 1-4 Total (n=178)
Alopecia	89 (50%)	0 (0%)	89 (50%)
Myalgia	79 (44%)	0 (0%)	79 (44%)
Fatigue	74 (42%)	2 (1%)	76 (43%)
Constipation	60 (34%)	0 (0%)	60 (34%)
Hand-Foot Skin Reaction[2]	56 (32%)	1 (1%)	57 (32%)
Nausea	53 (30%)	0 (0%)	53 (30%)
Decreased appetite	47 (26%)	2 (1%)	49 (28%)
Weight decreased	43 (24%)	0 (0%)	43 (24%)
Abdominal pain	33 (19%)	8 (5%)	41 (23%)
Diarrhea	38 (21%)	3 (2%)	41 (23%)
Lipase increased	21 (12%)	20 (11%)	41 (23%)
Vomiting	32 (18%)	1 (1%)	33 (19%)
Arthralgia	32 (18%)	0 (0%)	32 (18%)
Hypertension	22 (12%)	10 (6%)	32 (18%)
Dry skin	31 (17%)	0 (0%)	31 (17%)
Rash	31 (17%)	0 (0%)	31 (17%)
Muscle spasms	30 (17%)	0 (0%)	30 (17%)
Anemia	14 (8%)	13 (7%)	27 (15%)
Dyspnea	25 (14%)	2 (1%)	27 (15%)
Cough	26 (15%)	0 (0%)	26 (15%)
Headache	25 (14%)	0 (0%)	25 (14%)
Dizziness	23 (13%)	0 (0%)	23 (13%)
Back pain	20 (11%)	2 (1%)	22 (12%)
Blood bilirubin increased	15 (8%)	6 (3%)	21 (12%)
Pain in extremity	21 (12%)	0 (0%)	21 (12%)
Dysgeusia	18 (10%)	0 (0%)	18 (10%)
Hypomagnesaemia	18 (10%)	0 (0%)	18 (10%)
Pruritus	18 (10%)	0 (0%)	18 (10%)

Invictus Study Design

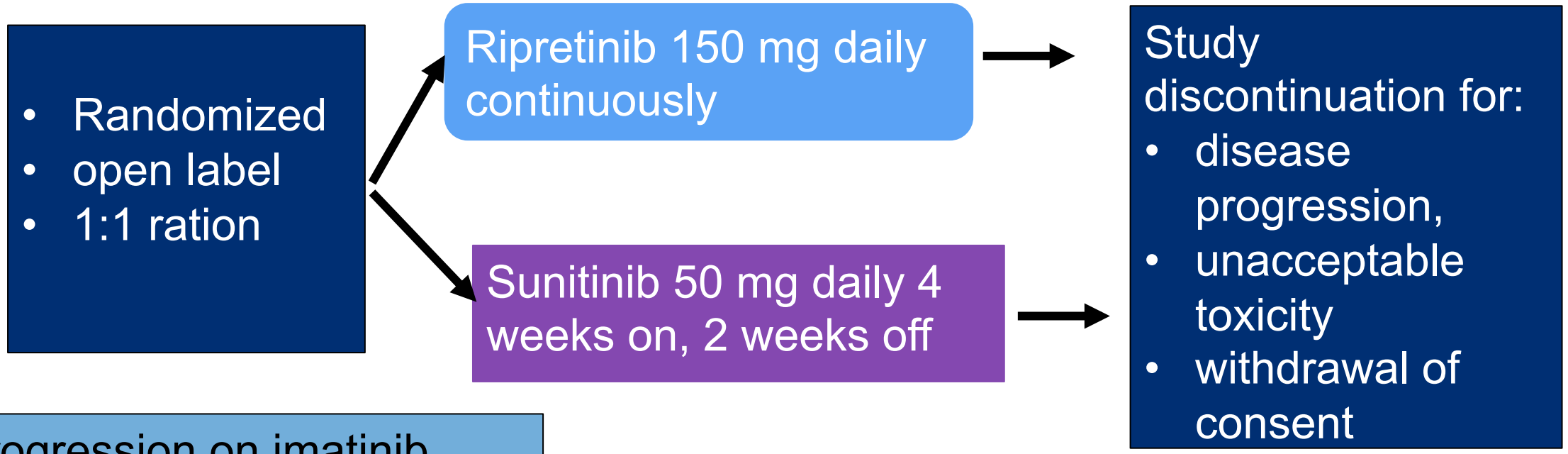


Press Release 8/13/19: Invictus Study Results

Outcome	Placebo	Ripretinib
Progression Free Survival	4.1 weeks	27.6 weeks
Change in risk of disease progression or death		Decreased by 85% (HR of 0.15, p<0.0001)
Overall Response Rate	0.0%	9.4% (p-value=0.0504)
Overall Survival	6.6 months	15.1 months (HR = 0.36, nominal p-value=0.0004)
Grade 3 or 4 treatment-emergent adverse events	44%	49%

Based on the **positive** **INVICTUS data**, Deciphera expects to submit a **New Drug Application** to the U.S. Food and Drug Administration for ripretinib for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib and regorafenib in **the first quarter of 2020.**

Intrigue: A Phase 3, Interventional, Randomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients with Advanced Gastrointestinal Stromal Tumors after Treatment with Imatinib

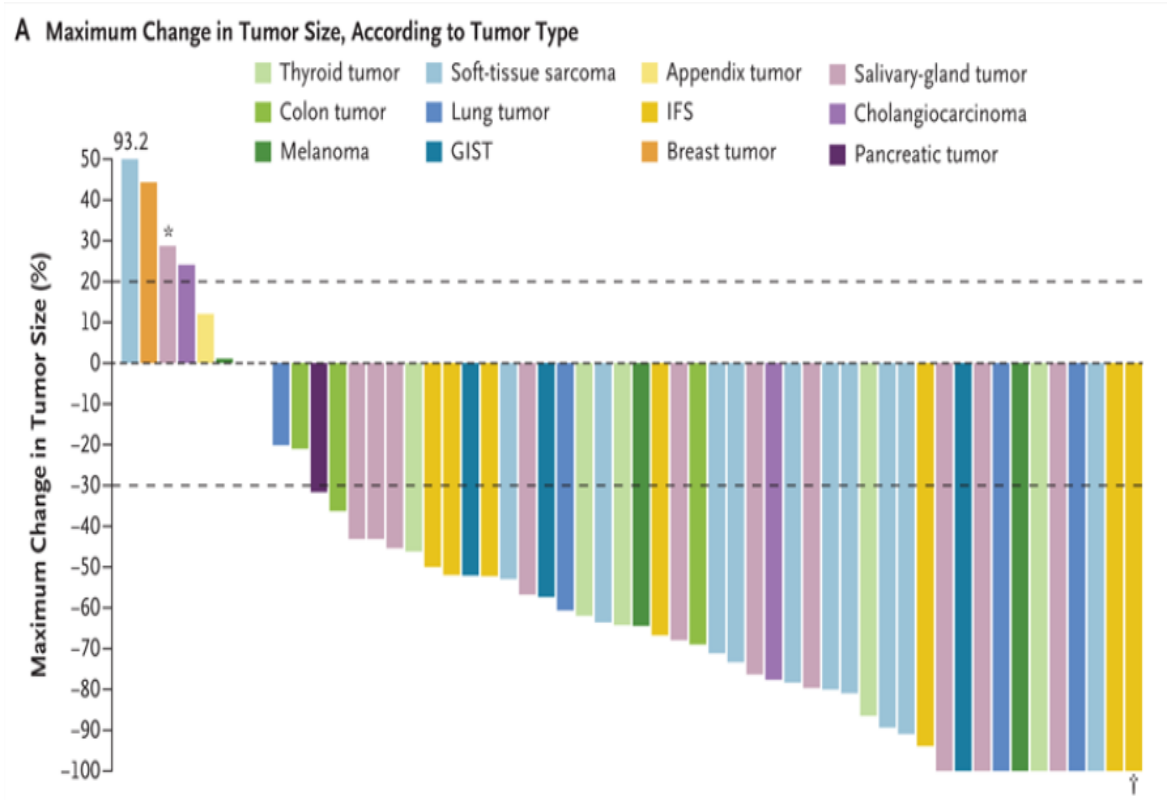


- Progression on imatinib
- Documented KIT/ PDGFRA mutation

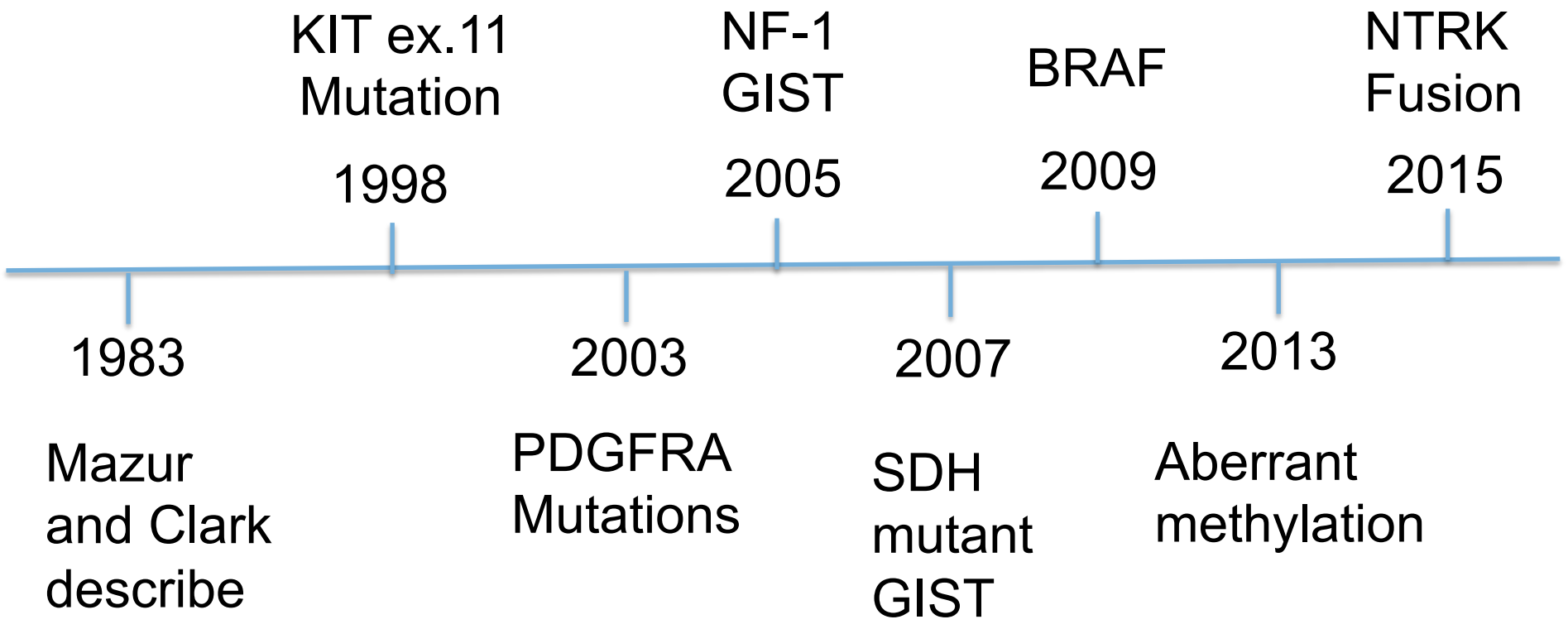
Study endpoints: PFS based on independent radiology assessment
Secondary endpoints: Response rate (RECIST and CHOI), Overall Survival, Quality of Life, Time to tumor progression, Safety profile.

Phase 1/2 trial of Larotrectonib

- Larotrectonib is an inhibitor of neurotrophic receptor tyrosine kinase proteins.
- Fusions with one of the 3 NTRK proteins is found in a diversity of tumors.
- Patients without response were found to not have NTRK fusions or have mutations affecting the kinase domain



Drilon A, Laetsch TW, Kummar S, et al. N Engl J Med 2018; 378(8):731-739.

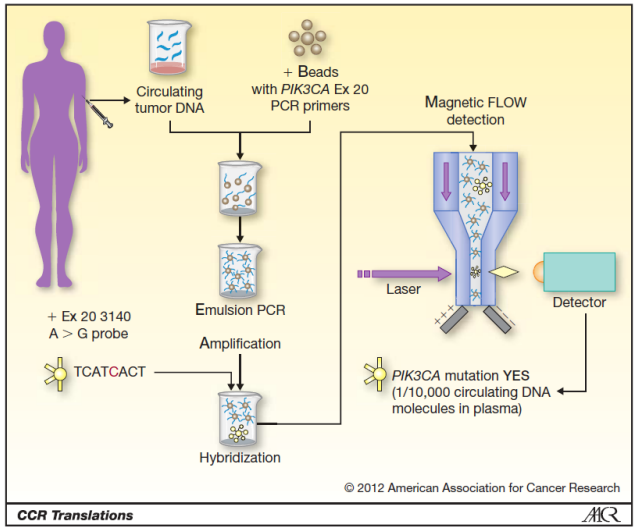

KIT ex.11
Mutation
1998
NF-1
GIST
2005
BRAF
2009
NTRK
Fusion
2015
1983
Mazur
and Clark
describe
GIST
2003
PDGFRA
Mutations
2007
SDH
mutant
GIST
2013
Aberrant
methylation

Future Directions

- Greater use of mutational testing for selection of therapy
  - How will we incorporate new agents
  - Therapies for NF-1 and SDH deficient GIST are needed
- Evaluation of combination therapies
- Evaluation of immunotherapy: checkpoint inhibitor therapies as well as cellular therapies

Future Directions

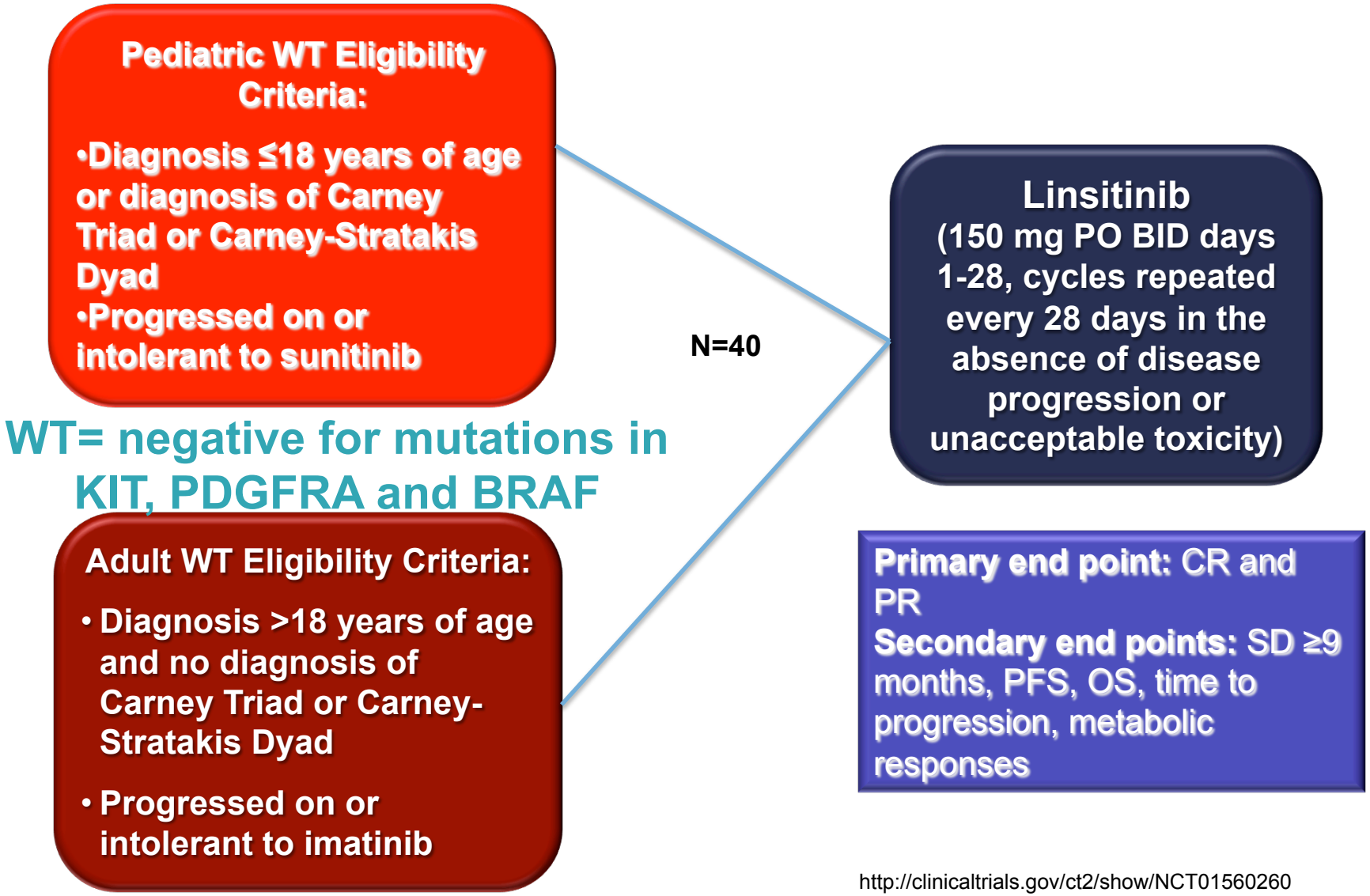
- Enhanced methods of assessing for resistance clones



Richardson AL, Iglehart JD. Clin Cancer Res 18: 3209–3211, 2012

Thank you for being able to Participate!

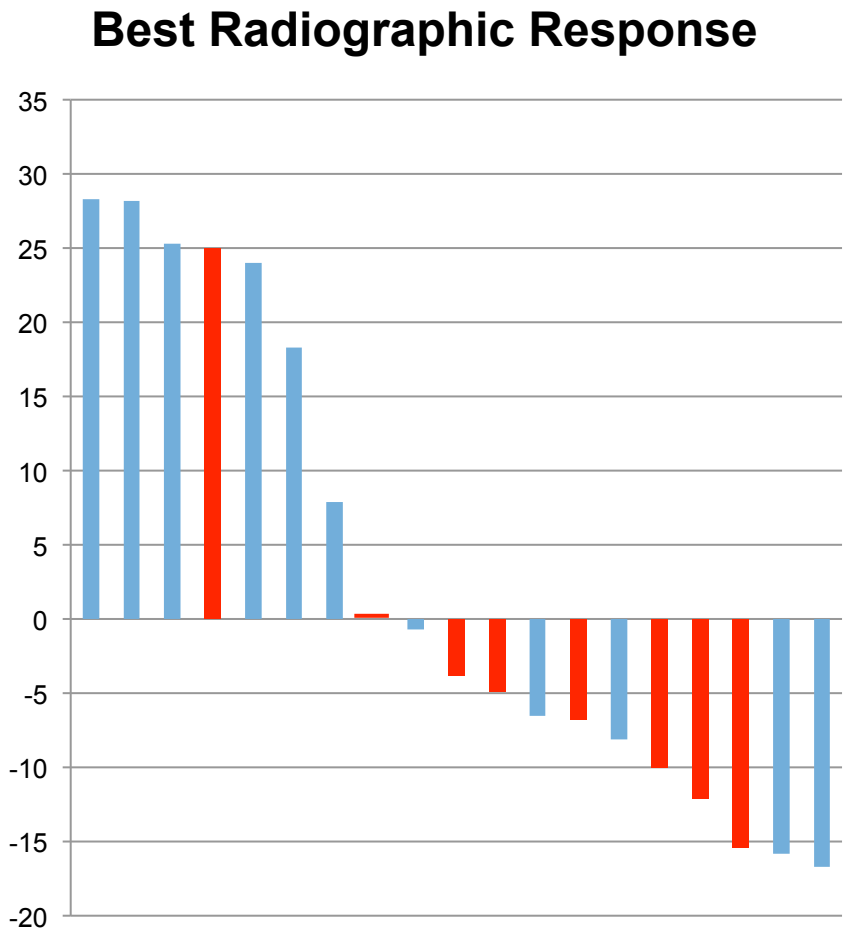
Phase 2 Study Design



http://clinicaltrials.gov/ct2/show/NCT01560260

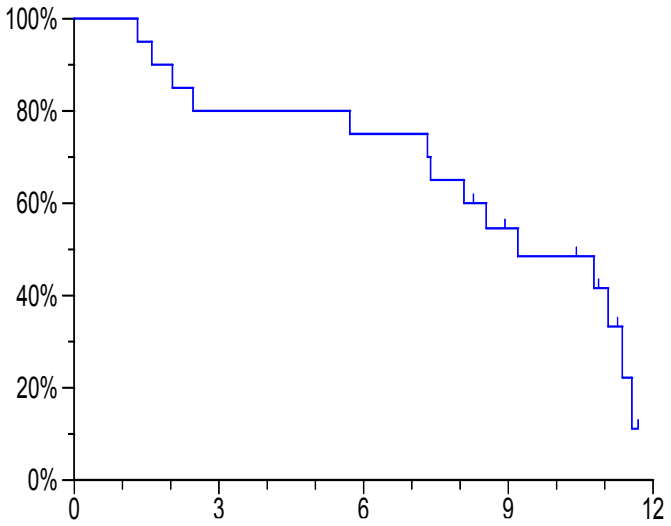
Response Data

RECIST 1.1 Response	N (20)	Total (%)
CR/PR	0	0%
SD	17	85%
CR/PR/SD ≥ 9 months	8	40%
PD	2	10%
NA	1	5%

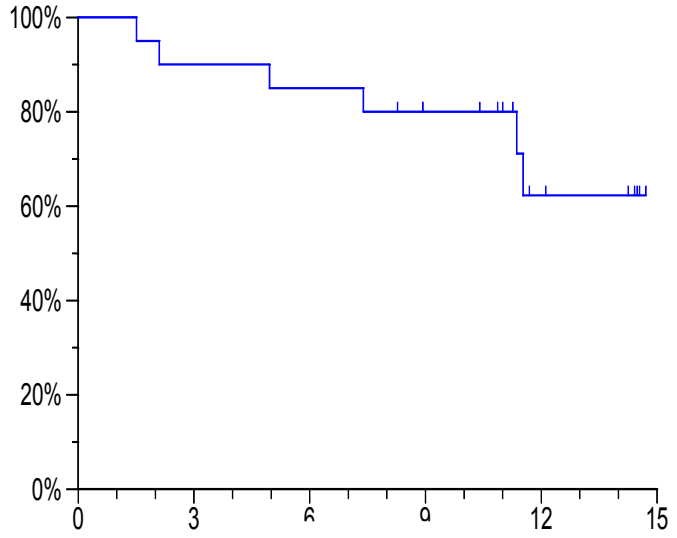


On study for 9 months or longer

PFS and OS



PFS, 9 Month Estimate: 55%
14/20 Events



OS, 9 Month Estimate: 80%
6/20 Events

Immunotherapy trials

- Nivolumab with or without Ipilumimab in Treating Patients with Metastatic Sarcoma that cannot be removed by Surgery (NCT02500797)
- Combination of MK3475 and Metronomic Cyclophosphamide in Patients with Advanced Sarcoma: Multicenter Phase II trial (PEMBROSARC), (NCT02406781)
- A Phase II study of Nivolumab plus Ipilumimab in Non-Resectable Sarcomas and Endometrial Carcinoma (NCT02982486)

Clinical Trials in “Wild Type GIST”

Vandetanib

- No responses

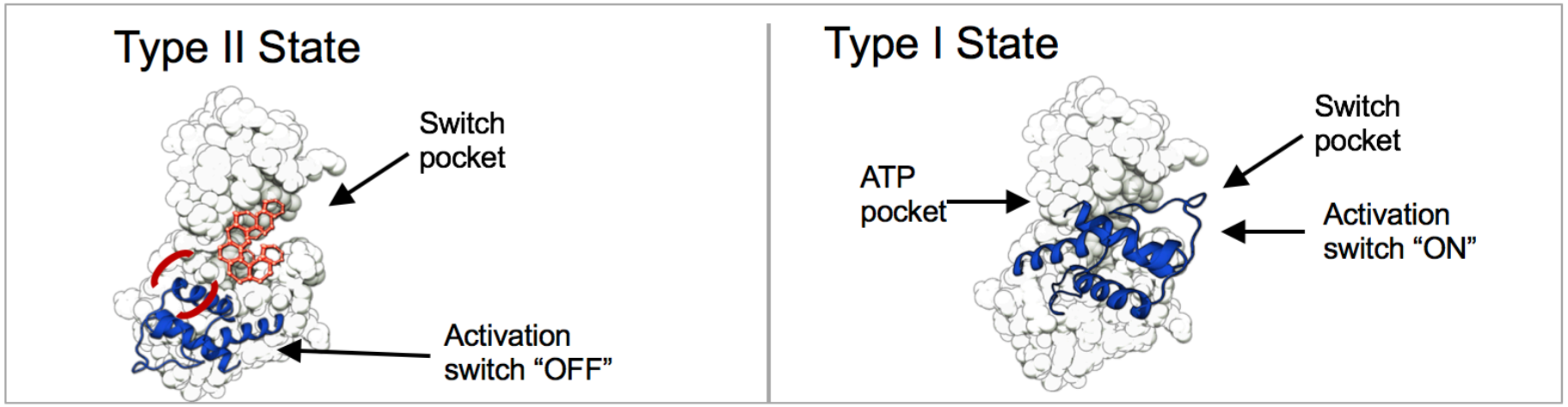
Guanecitadine

- Ongoing at the NCI

Temazolamide

- To be activated soon

Ripretinib (DCC-2816) Mechanism of Action



T II agonist **Pull**

Switch Control Inhibitors provide micropockets to attract Switches

- **Role reversal: Inhibitor functions as "pocket", stabilizing the Ligand in the OFF state**

T I antagonist **Push**

Switch Control Inhibitors compete with Switch for the Switch pocket

- **Eject/compete with Switch Ligand for Pocket**
- **Classical ligand antagonist concept**

Think of this as a "Push-Pull" mechanism for inhibiting kinases