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MD Anderson Cancer Center
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Novel Approaches to Treatment of Gastrointestinal Stromal Tumor (GIST)

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DISCLOSURE

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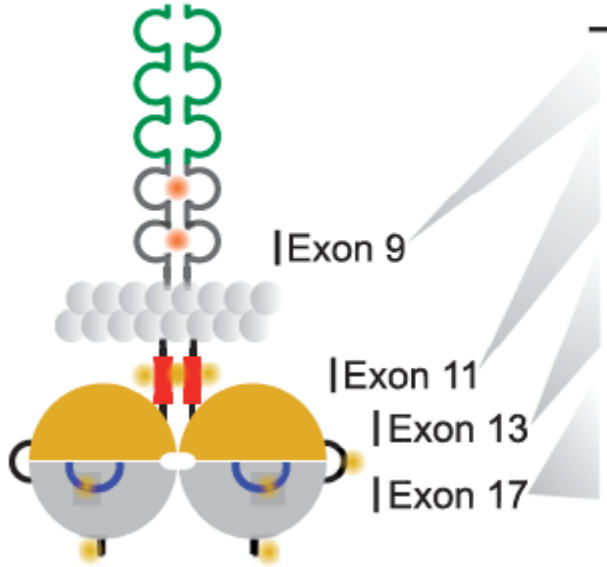
GIST BACKGROUND

- KIT mutations drive ~80% of GISTs
- Majority of patients with KIT primary mutations respond to 1st line imatinib but resistance develops most commonly due to secondary mutations in KIT
- Approved 2nd and 3rd line agents (sunitinib and regorafenib) confer modest clinical benefit compared with imatinib likely due to multiple drug-resistant mutations arising in individual tumors
- Unmet medical need for agents that can address breadth of primary/secondary KIT mutations across lines of therapy



Domain	Gene	1° Mutation Frequency	2° Mutation Frequency
D5	*KIT*	10%	
JM	*KIT*	67	
	PDGFRA	1	
TK1	*KIT*	1	56
	PDGFRA	1	
A-Loop	*KIT*	1	41
	PDGFRA D842V	5	
	PDGFRA	1	3

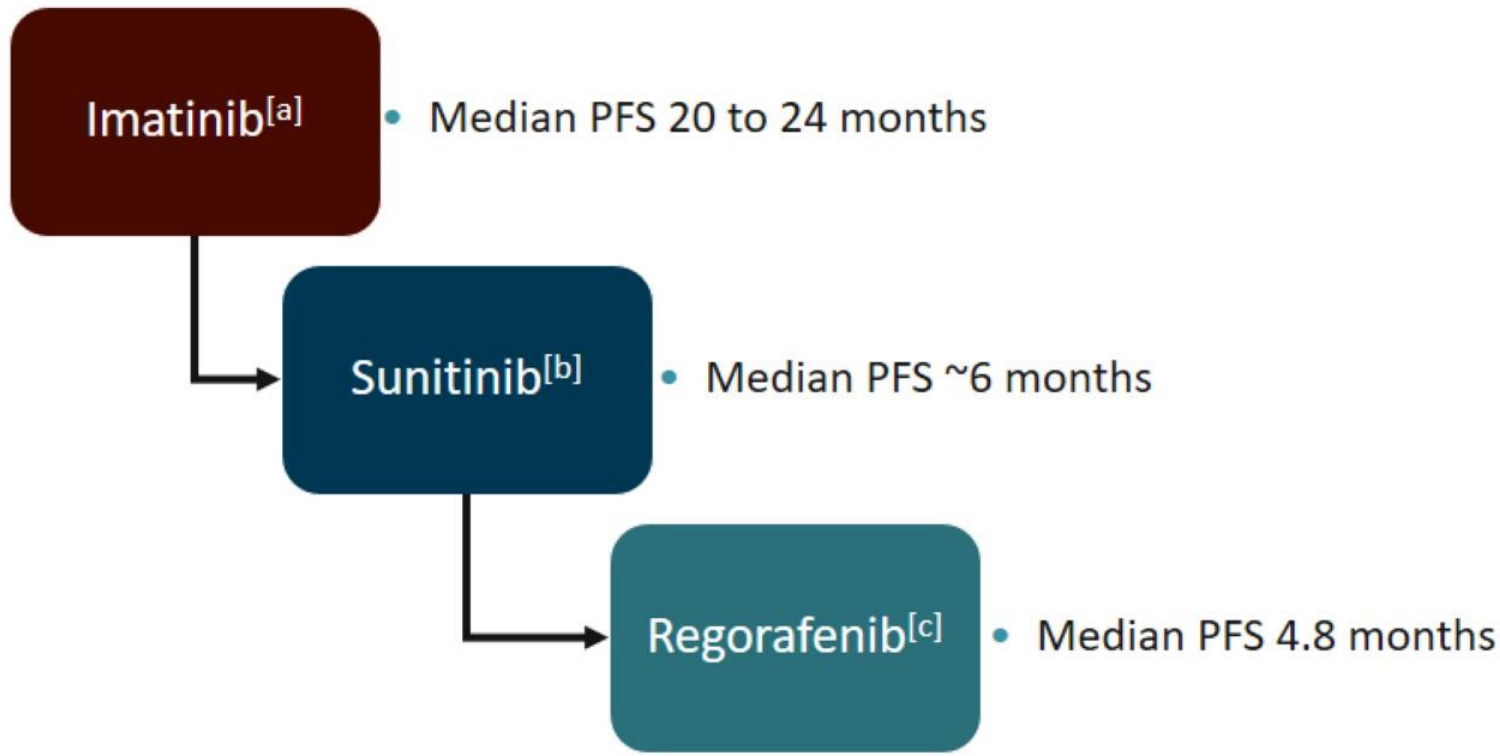
Other important GIST subgroups:

- NF1-mutated
- SDH-mutated
- BRAF/KRAS-mutated
- Quadruple-negative (KIT/PDGFRA/SDH/RAS -wild-type)

Hemming M et al. Ann Oncol; 0:1-9, 2018.

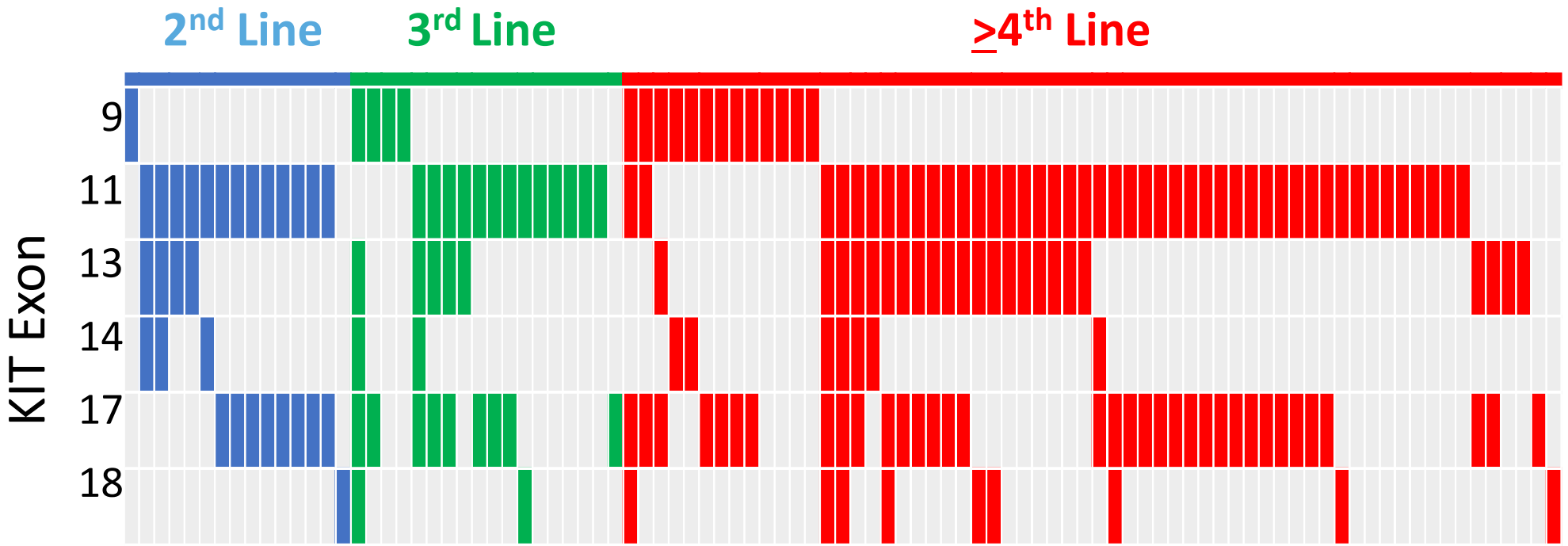
Unmet Medical Need in GIST

- Diminishing returns on kinase inhibition due to development of resistant mutations



a. Casali PG, et al. *J Clin Oncol*. 2017;35:1713-1720;
b. Demetri GD, et al. *Lancet*. 2006;368:1329-1338;
c. Demetri GD, et al. *Lancet*. 2013;381:295-302.

Liquid Biopsies (NGS) Detect Broad Spectrum of KIT Mutations in Previously Treated GIST

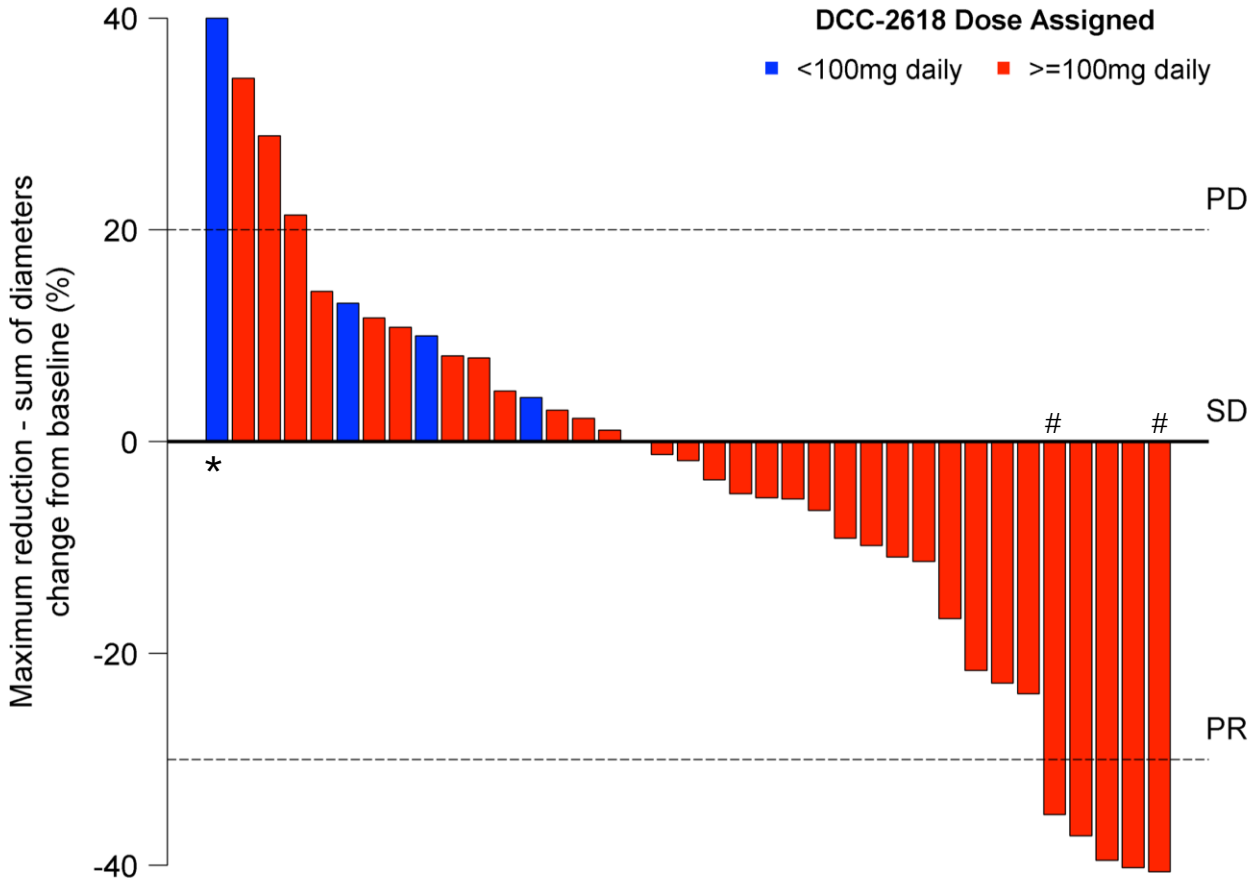


- Each column represents an individual patient
- In pts where a KIT mutation was detected in baseline ctDNA, secondary KIT mutations in exon 13, 14 17 and 18 were found across 2nd to ≥4thline pts.

George , Janku. ASCO 2018

Investigational Approaches
Ripretinib (DCC-2618)

- Selective KIT and PDGFRA switch-control inhibitor[a]
- Phase 1 study
  - Efficacy in 4th-line
    - ORR 9%; mPFS 24 weeks



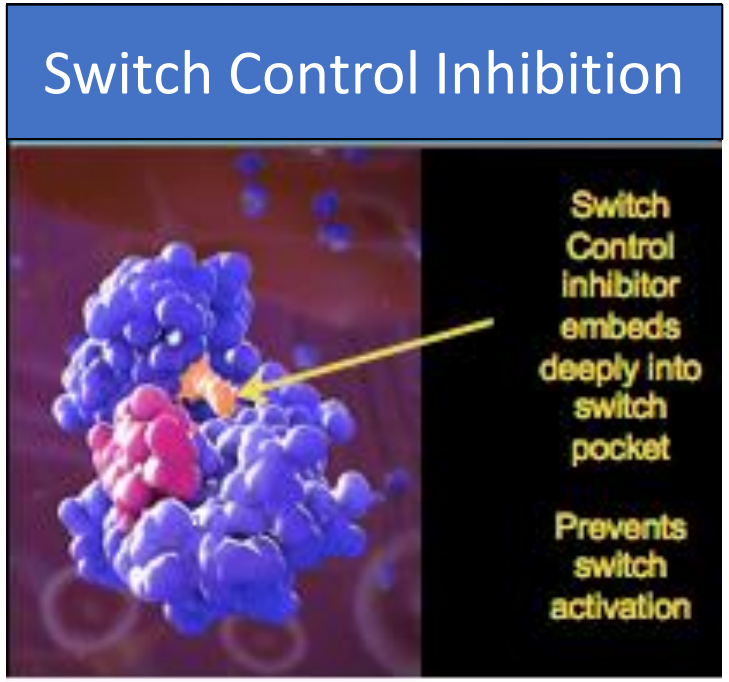
PD = Progressive disease, SD = Stable disease, PR = Partial response
*66% increase in tumor size; #PR at RP2D

Janku, George ESMO 2017
George, Janku ESMO 2018

RIPRETINIB (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

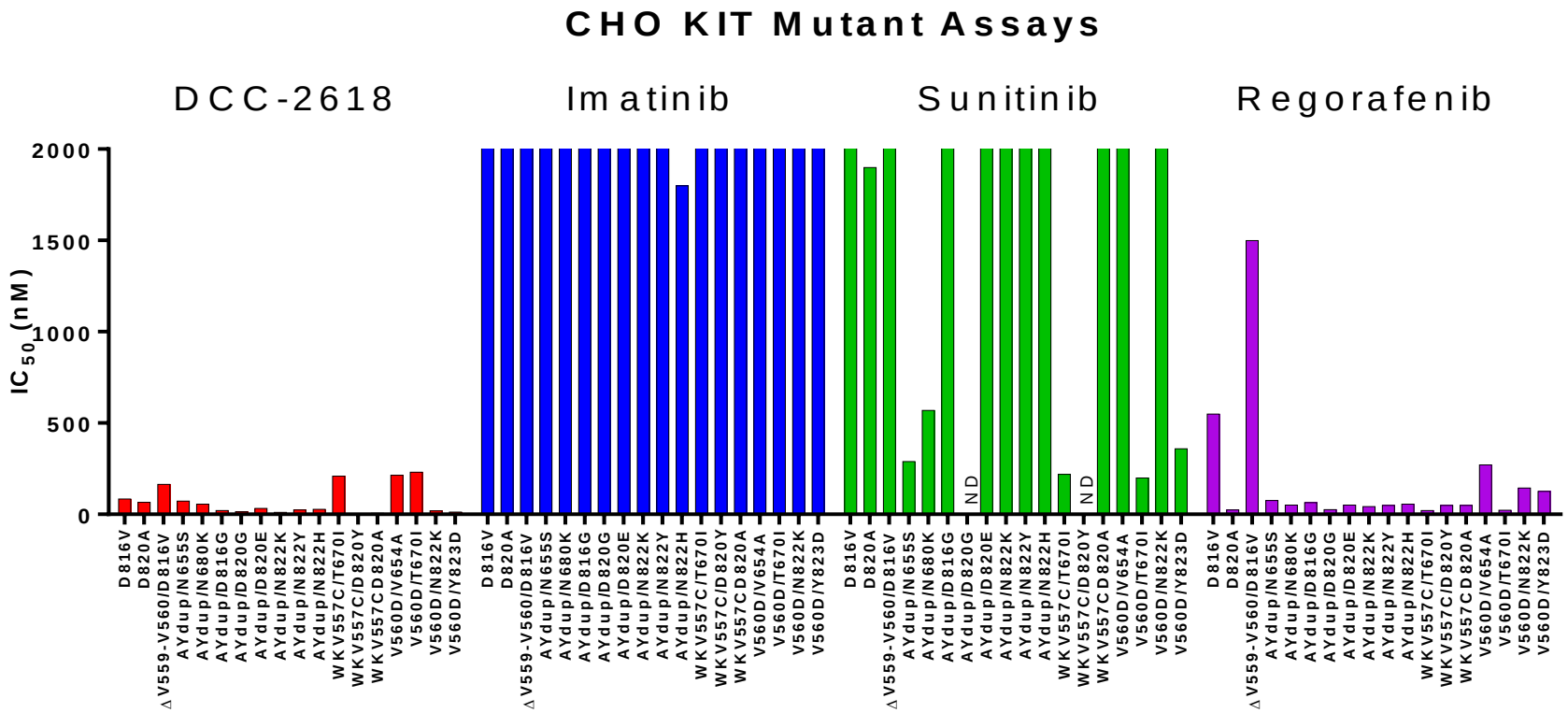
- DCC-2618 was designed to potently inhibit a broad range of mutations in *KIT* and *PDGFRA* kinases



- 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*

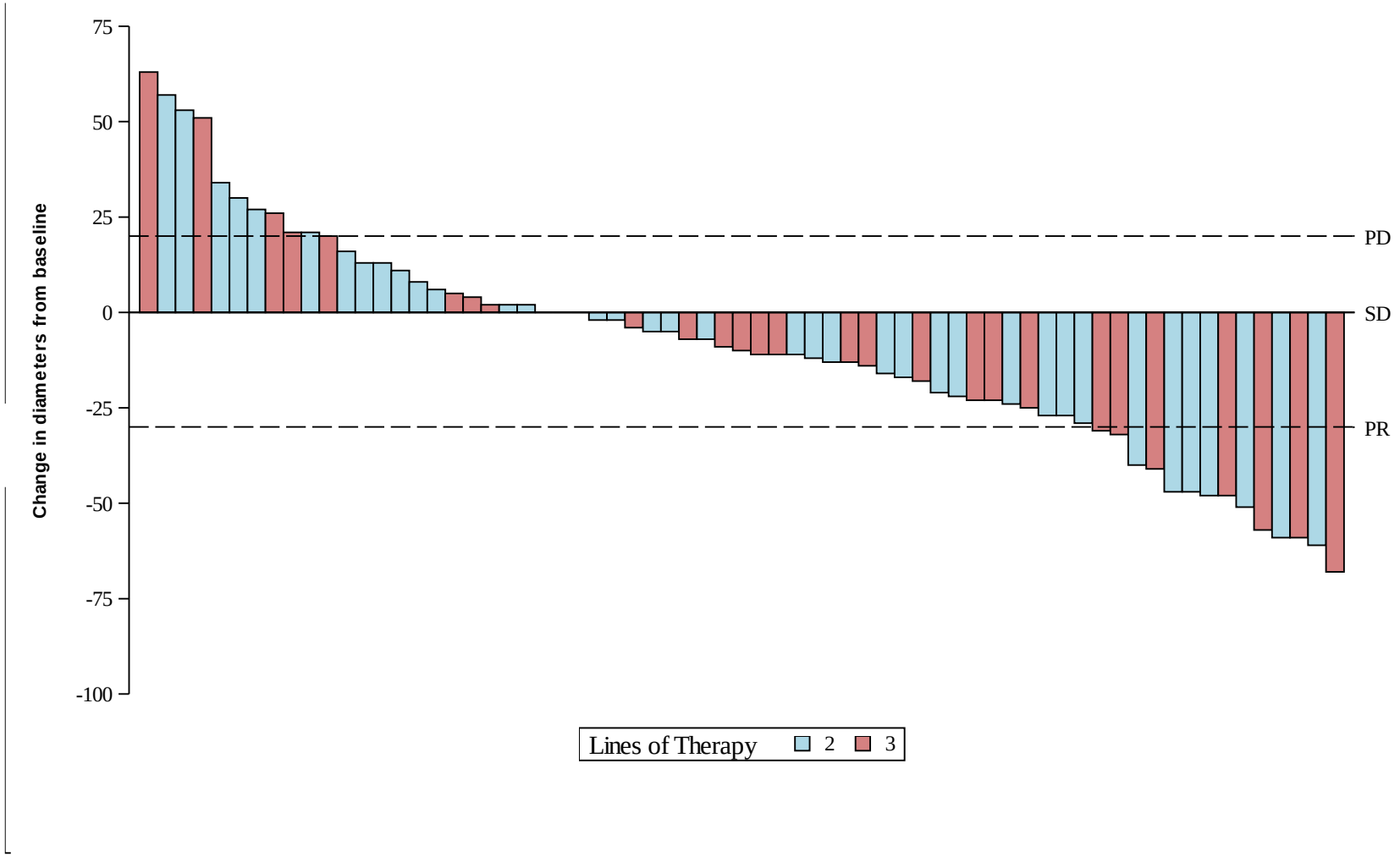
RATIONALE FOR DCC-2618 STUDY

- 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
  - IC_{50} for *KIT* T670I 221 nM , IC_{50} for 189 nM for *KIT* V654A



Janku, George ENA 2016
Smith. Cancer Cell 2019

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

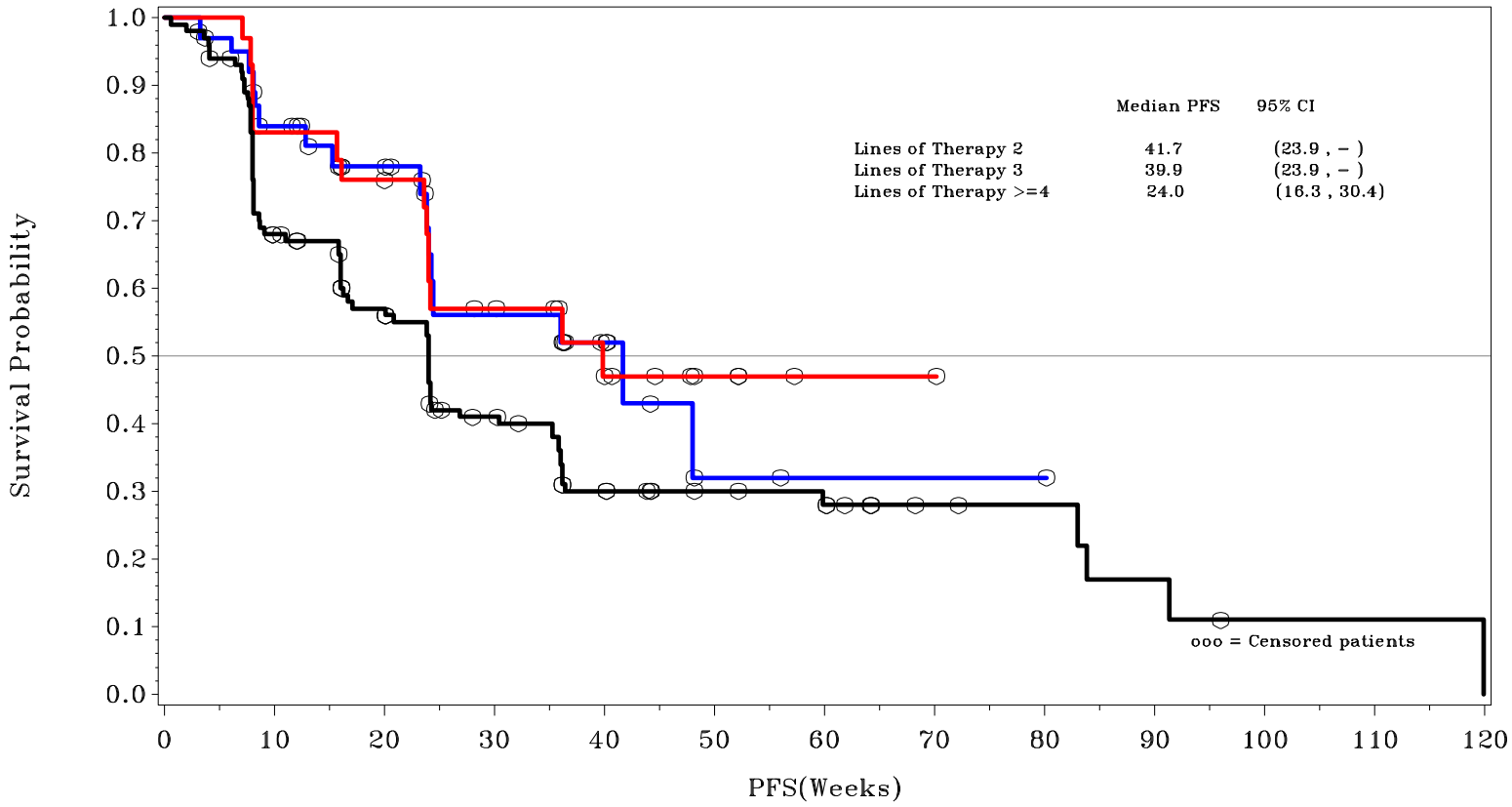
George, Janku ESMO 2018

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

mPFS by Line of Therapy - Patients at ≥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 IPDE, 63% (n=29) and 28% (n=13) of patients stayed on study for >8 and >16 weeks, respectively

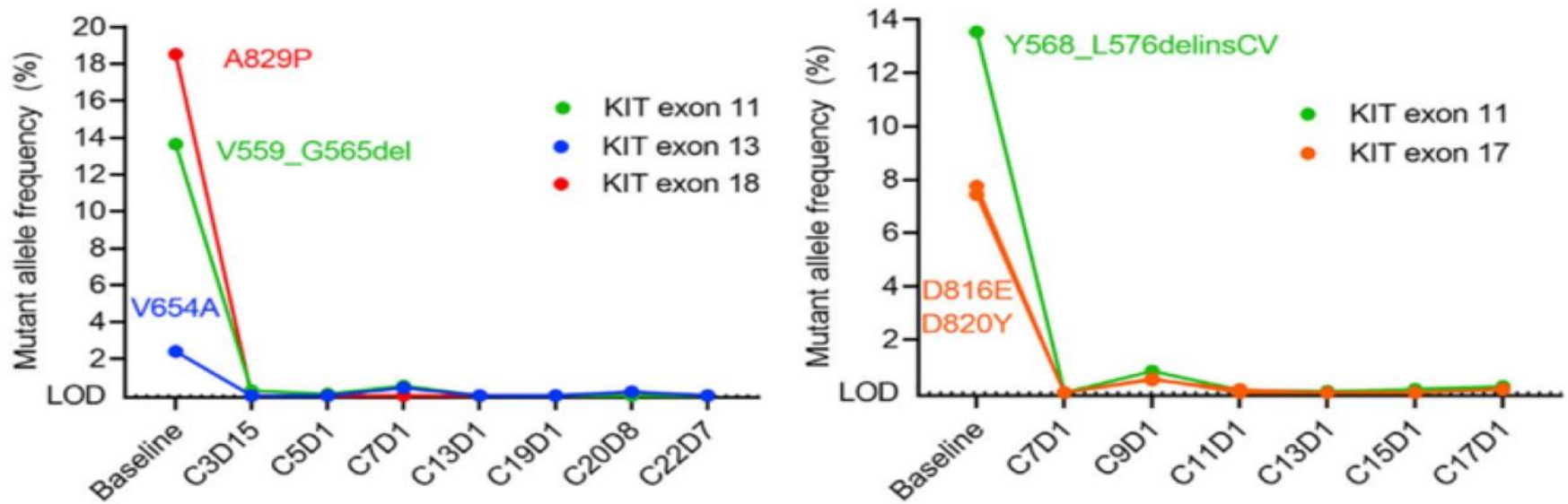


2nd Line	**38**	**30**	**21**	**13**	**8**	**2**	**1**	**1**	**1**	**0**	**0**	**0**	**0**
3rd Line	29	24	21	14	8	4	1	1	0	0	0	0	0
≥4th Line	111	71	53	32	20	14	12	6	5	3	1	1	0

George, Janku ESMO 2018

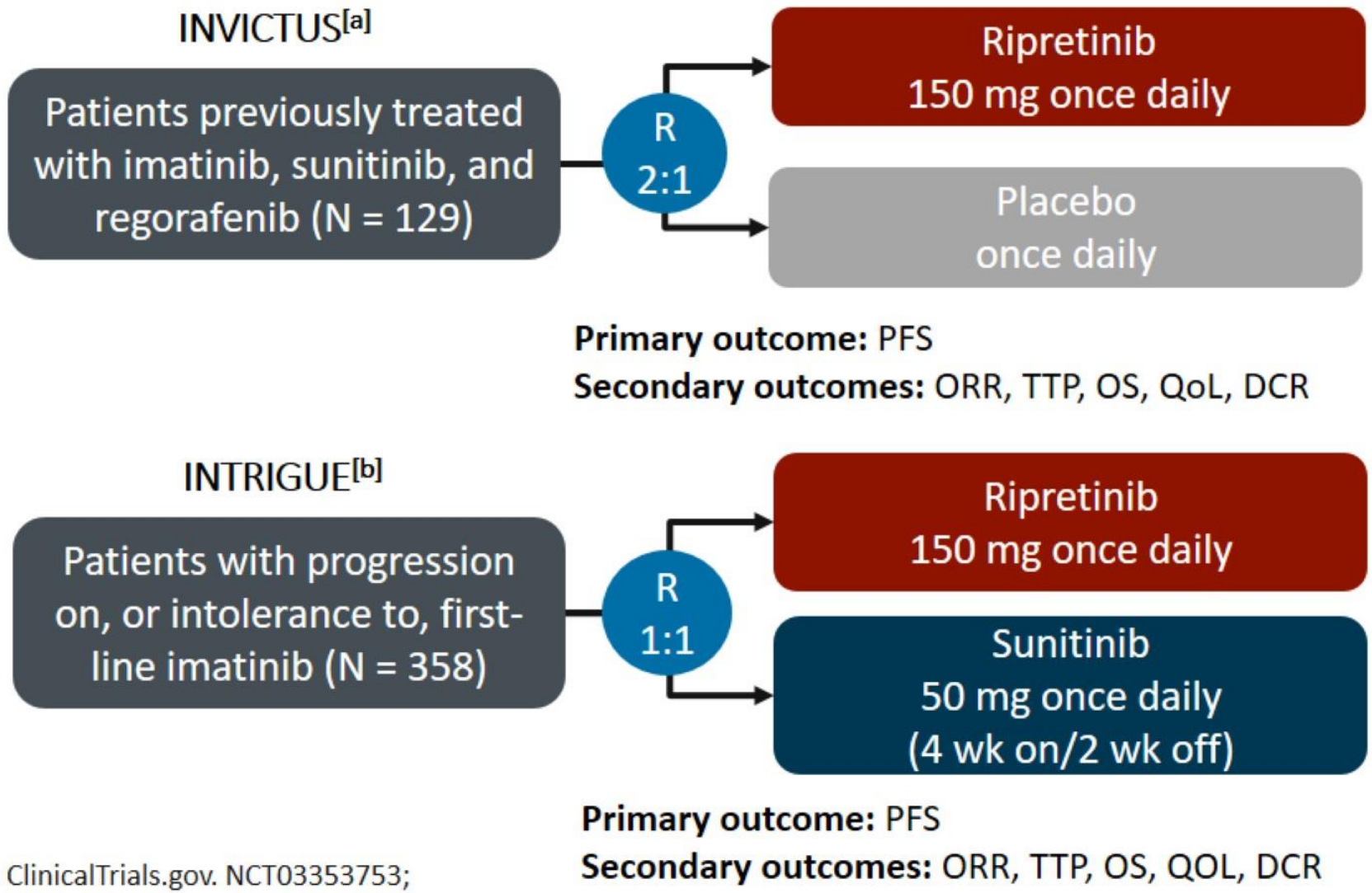
Liquid Biopsy to Monitor Treatment Response With New Therapies

ctDNA-Assessed Mutant Allele Elimination With Ripretinib in 2 Patients With Resistant *KIT* Mutations



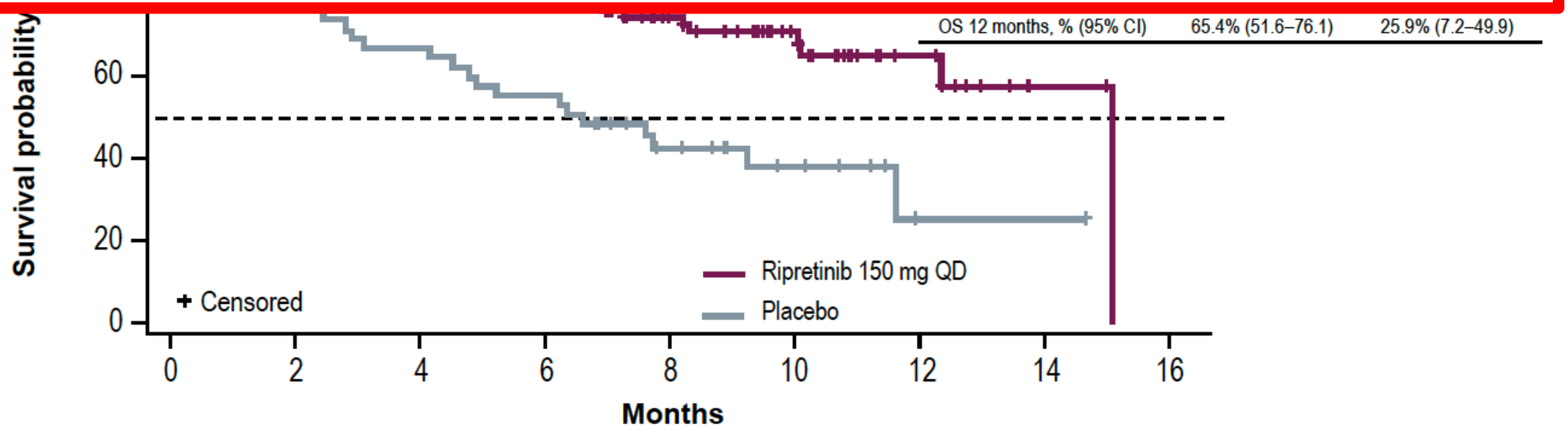
Smith BD, et al. *Cancer Cell*. 2019;35:738-751.e9.

Phase 3 Trials of Ripretinib in GIST



a. ClinicalTrials.gov. NCT03353753;
b. ClinicalTrials.gov. NCT03673501.

TIME FROM FIRST PATIENT DOSED IN PHASE I TO PHASE III DATA PRESENTATION ~ 3.5 YEARS

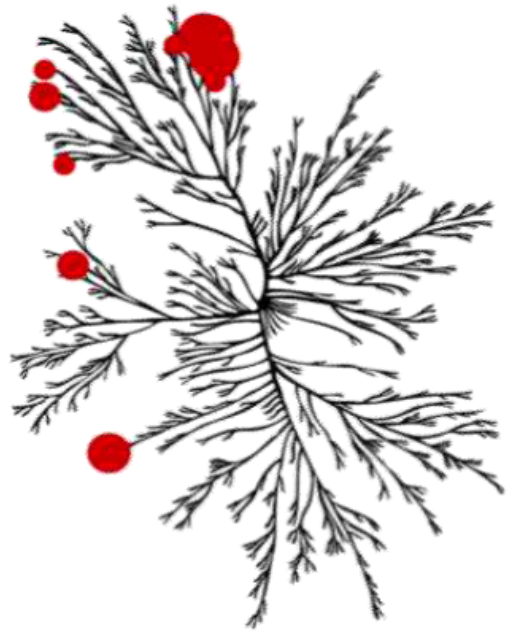


Number of patients at risk:									
Ripretinib 150 mg QD	85	81	76	67	42	24	10	2	0
Placebo	44	34	29	24	14	8	1	1	0

Von Mehren M, et al. *Ann Oncol.* 2019;30: Abstract LBA87.

Avapritinib: a highly selective and potent KIT/PDGFRA inhibitor for GIST

GIST mutation(s)		Medical need by mutation	Avapritinib biochemical IC_{50}[1]
KIT Exon 11 deletion	JM domain	1L imatinib is effective 2L sunitinib/3L regorafenib have low ORR/short PFS	0.6 nM
KIT Exon 11 V560G			1 nM
KIT Exon 11/13	ATP binding site	Approved 2L/3L agents have low ORR/short PFS	11 nM
KIT Exon 11/14			28 nM
KIT Exon 11/17	Activation loop		0.1 nM
PDGFRα D842V		No highly effective therapy in any line	0.24 nM



Avapritinib kinome selectivity

Clinical Trials

NAVIGATOR GIST

Phase 1 advanced GIST

VOYAGER GIST

Phase 3 trial of avapritinib vs. regorafenib in 3L and 4L GIST

Adapted from Heinrich CTOS 2018

NAVIGATOR: Phase I study of Avapritinib in refractory GIST

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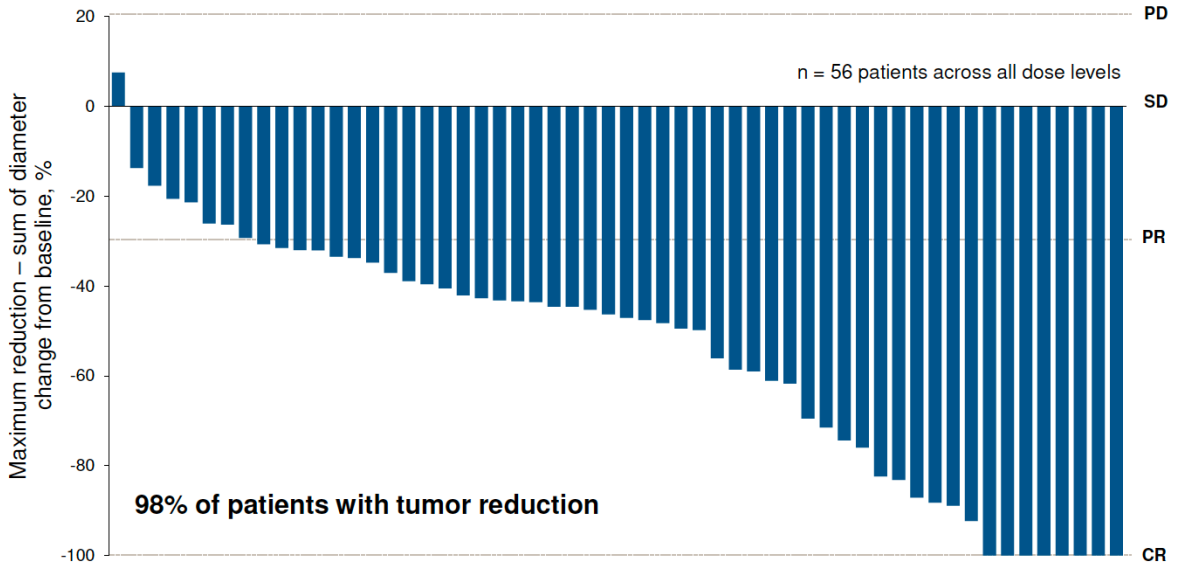
Best response by central radiology in PDGFRα D842V GIST



PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

	PDGFRα D842V n = 56	≥4L all patients n = 109	3L/4L regorafenib-naïve non-D842V n = 23	2L non-D842V n = 20
ORR (central radiology), % (n) [95% CI]	84% (47) [72-92]	20% (22) [13.1-29.0]	26% (6) [10.2-48.4]	25% (5) [9-49]
mDOR (central radiology), months [95% CI]	NE [NE, NE]	7.3 [7.2-NE]	10.2 [4.2-NE]	NR
CBR (central radiology), % (n) [95% CI]	96% (54) [88-100]	40% (44) [31.1-50.2]	70% (16) [47.1-86.8]	NR
mPFS (central radiology), months [95% CI]	NE [NE, NE]	3.7 [3.5-5.6]	8.6 [5.6-14.7]	NR
mPFS (investigator), months [95% CI]	22.8 [20.8-28.4]	5.5 [3.8-6.8]	10.2 [5.7-NE]	NR
Benchmarks	**PDGFRα D842V** Approved agents: ORR ~0% mPFS ~3 mo mOS ~15 mo	**4L** imatinib re-treatment: ORR ~0% PFS 1.8 mo	**3L** regorafenib: ORR ~5% PFS 4.8 mo	**2L** sunitinib: ORR ~7% PFS 6 mo

NR, not reported; mPFS, median progression-free survival; mOS, median overall survival.

ORR is not an endpoint for 2L but is early signal readout.

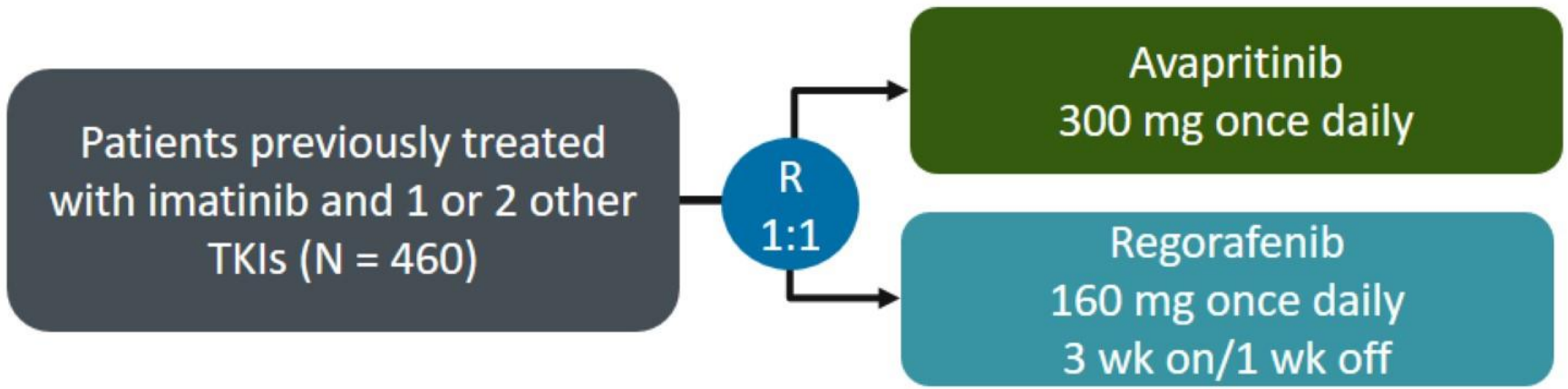
- Phase 1 NAVIGATOR study[b]
  - Efficacy
    - PDGFRA exon 18 (n = 43): CBR 95%; ORR 86%; mDOR NR
    - ≥ 4th-line (n = 111): CBR 41%; ORR 22%; mDOR 10.2 mo
  - Safety
    - Grade 3/4 TRAEs: anemia (16.2%), fatigue (6.4%), bilirubin increase (3.9%), cognitive effects (3.9%), diarrhea (2.9%)

b. Heinrich MC, et al. ASCO® 2019. Abstract 11022.

Adapted from Heinrich CTOS 2018 and ASCO 2019

VOYAGER

Phase 3 Trial of Avapritinib in 3rd and 4th-Line GIST



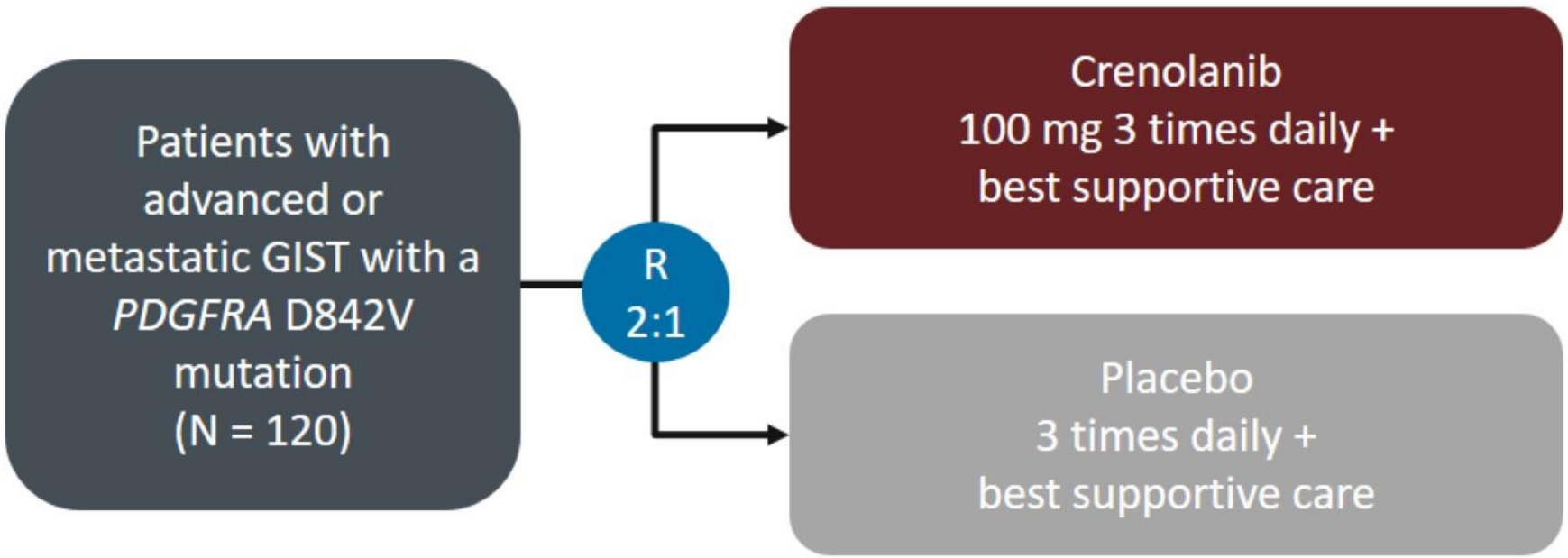
Primary outcome: PFS
Secondary outcomes: ORR, OS, QoL

- Additional clinical trials are planned, including a 2nd-line trial vs sunitinib that includes genotype testing

ClinicalTrials.gov. NCT03465722.

CrenoGIST

Phase 3 Trial of Crenolanib in D842V-Mutated GIST



Primary outcome: PFS

Secondary outcome: OS

ClinicalTrials.gov. NCT02847429.

CONCLUSIONS

- ✓ Despite GIST being an early poster child for personalized cancer therapy therapeutic resistance is a significant problem for existing targeted therapies (imatinib, sunitinib, regorafenib)

- ✓ Understanding the biology of resistance is critical for developing new therapies

- ✓ Development of novel type I KIT/PDGFRA inhibitor Avapritinib (BLU-285, FDA Approved) and switch pocket KIT/PDGFRA inhibitor Ripretinib (DCC-2618, FDA NDA submitted) will likely significantly expand therapeutic options for patients with resistant GIST

- ✓ Ripretinib experience demonstrated potential of liquid biopsies in the drug development process

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