What's New For GIST Patients

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The Emerging Role of Circulating Tumor DNA in Gastrointestinal Stromal Tumor

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NCI Comprehensive Cancer Center
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- Most common **GI sarcoma**
  - 1-2% of all primary GI malignancies
  - 4500-6000 cases annually in US
- Treated with **tyrosine kinase inhibitors**
  - Prevalence > incidence
    - Clinical course >10-15yr (from pre-TKI era <12 mo)
- Peak incidence 40-60 yo
  - GISTs unusual in pts <40yo
  - M = F predominance
- High frequency of **metastatic disease,** commonly abdominal

GIST OVERVIEW

Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020:4, 66-73.
Søreide, Kjetil et al. *Cancer epidemiology* vol. 40 (2016): 39-46.

KIT

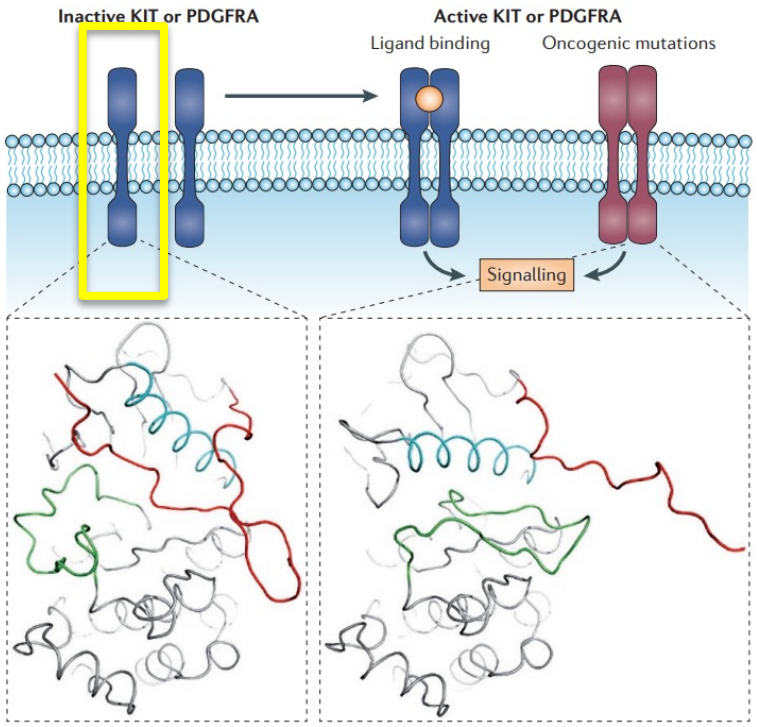
- 70-80% of GISTs
- Constitutive activation
- Most-common = exon 11, exon 9
- In-frame del*, insertions, substitutions, or combo

PDGFRα

- 5-10% of GISTs
- Constitutive activation
- Most-common = exon 12, exon 14, exon 18

KIT/PDGFR WILD TYPE

- 10-15% of GISTs
- *RAF, RAS, SDH, NTRK*



***KIT* and *PDGFRA* structure and mutations.**

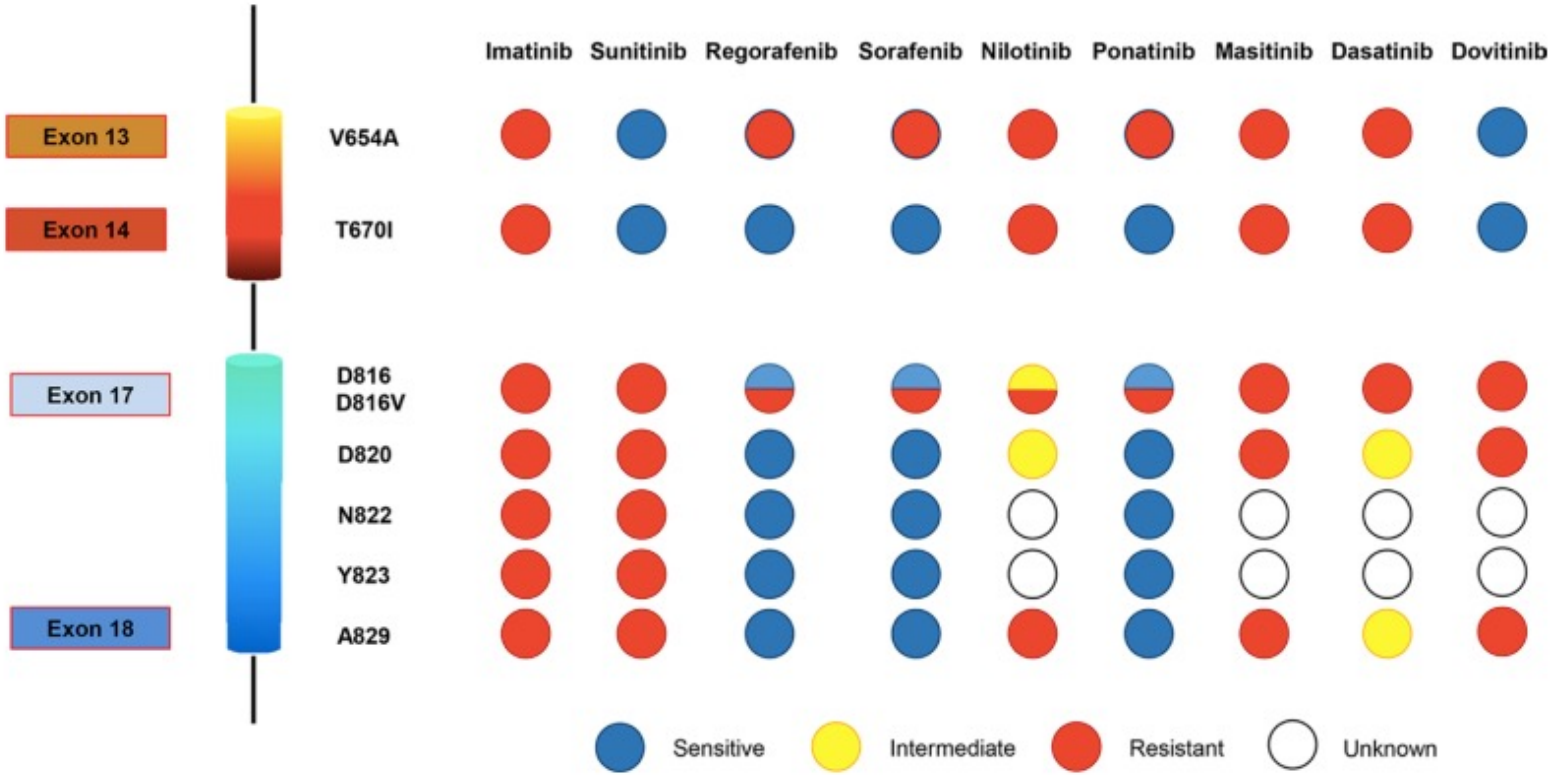
GIST DRIVER MUTATIONS

Christopher Corless, Christine Barnett, and Michael Heinrich. *Nature Reviews Cancer*. 2011: 11, 865-878.
Incorvia et al. *Cancers*. Feb 2021.

- *KIT* exon 11: imatinib 400 mg
- *KIT* exon 9: imatinib 800mg (or tolerated dose)
- *PDGFR* D842V: avapritinib
- *SDH* deficiency: sunitinib or regorafenib (TMZ trial)
- *RAF* V600E: RAF inhibitor
- *NF-1, RAS*: RAF or MEK inhibitor
- *PI3K*: mTOR inhibitor
- *IGF-1R* expressing – IGF-1R inhibitor trial
- *TRK* fusion – larotrectenib (NTRK inhibitor)
- ***KIT* resistance mutations**
  - **Exon 13** (ATP binding site): sunitinib 37.5 mg daily
  - **Exon 17** (A-loop): regorafenib or ripretinib

GIST TREATMENT BY SUBTYPE

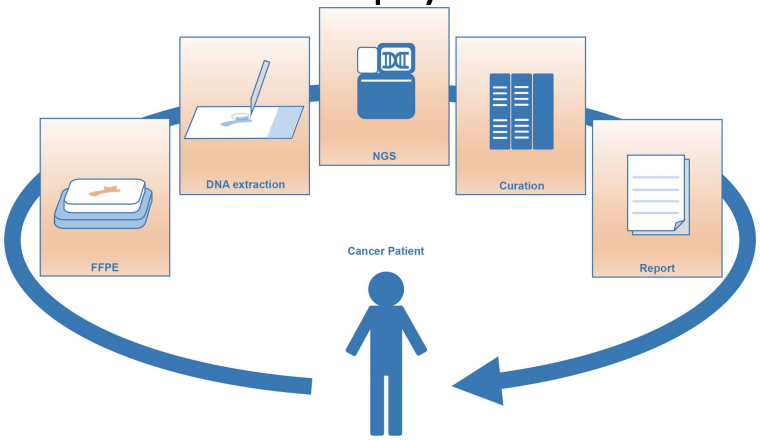
Jon Trent, MD PhD. *Miami Precision Medicine*. Apr 2022.



KIT SECONDARY MUTATIONS

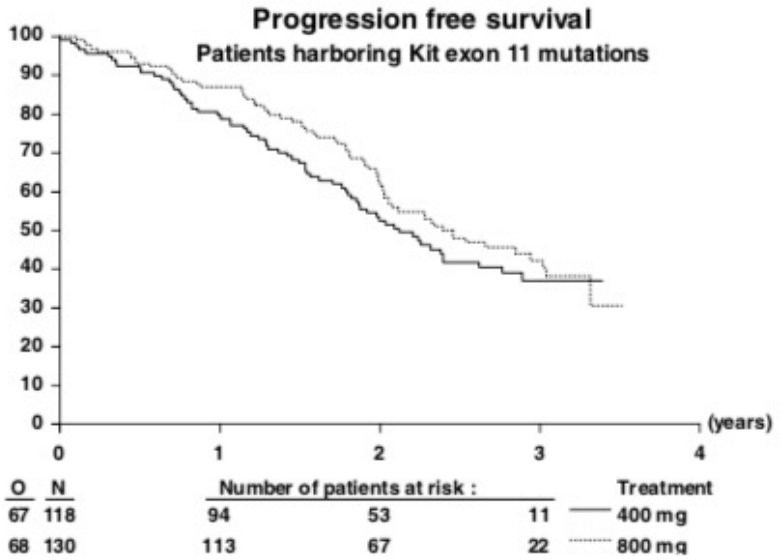
Serrano et al. *Oncotarget*, 2019, Vol. 10, (No. 59), pp: 6286-6287

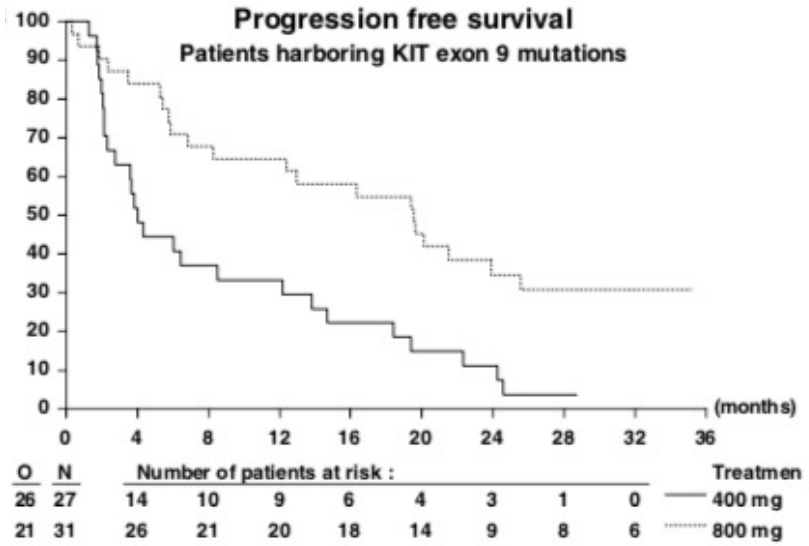
- **Optimal therapy for GIST patients requires mutation testing.**
- **Comprehensive, effective** in identifying tumor mutations
- Performed commonly on pretreatment tumor biopsy and resection specimens
- **Invasive**, requires adequate tissue quantity
- **Lengthy** turnaround times



MOLECULAR DIAGNOSTIC TESTING

Boonstra et al. *Oncotarget*. 2018; 9:13870-13883.
Nagahasi et al. *Cancer Science*. 2019;110:6–15.

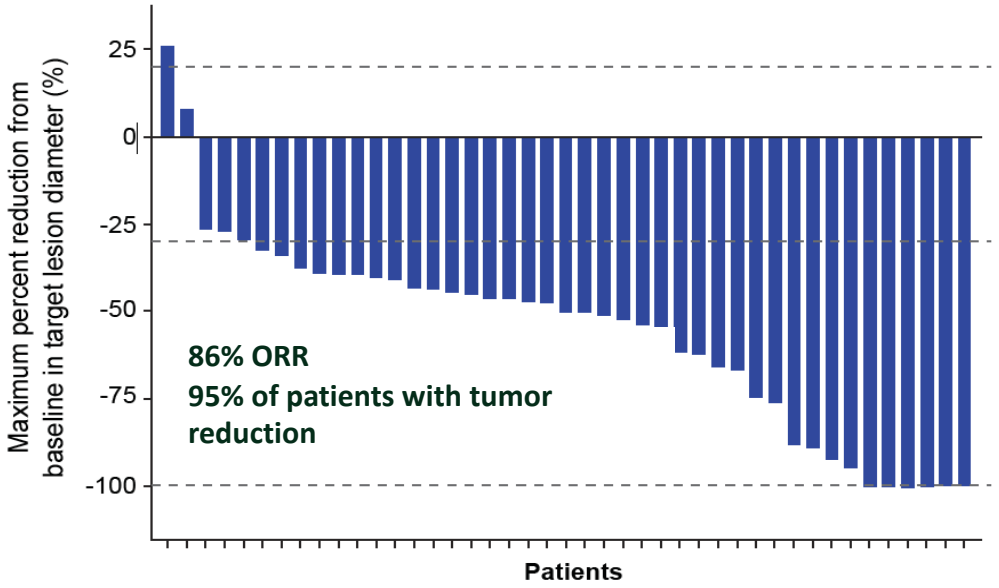




	Imatinib 800mg	Imatinib 400mg
Exon 9 mPFS	**20 months**	**4 months**
Exon 11 mPFS	30 months	27 months
Overall mPFS	27 months	24 months

NGS/GIST: *KIT* EXON 11 VS EXON 9

Debiec-Rychter et al. *European Journal of Cancer.* May 2006.



Best Response	PDGFRA Exon 18 (n=43)
CR	3
PR	34 (1 pending)
SD	5
PD	1
ORR (CR+PR), % (95% CI)	86.0 (72.1–94.7)
CBR,% (95% CI)	95.3 (84.2–99.4)
DOR,months (95% CI)	NE (11.5–NE)
PFS, months (95% CI)	NE (13.4–NE)

- NAVIGATOR study with BLU-285
- Antitumor activity with **avapritinib** in patients with **PDGFR D842V** mutation

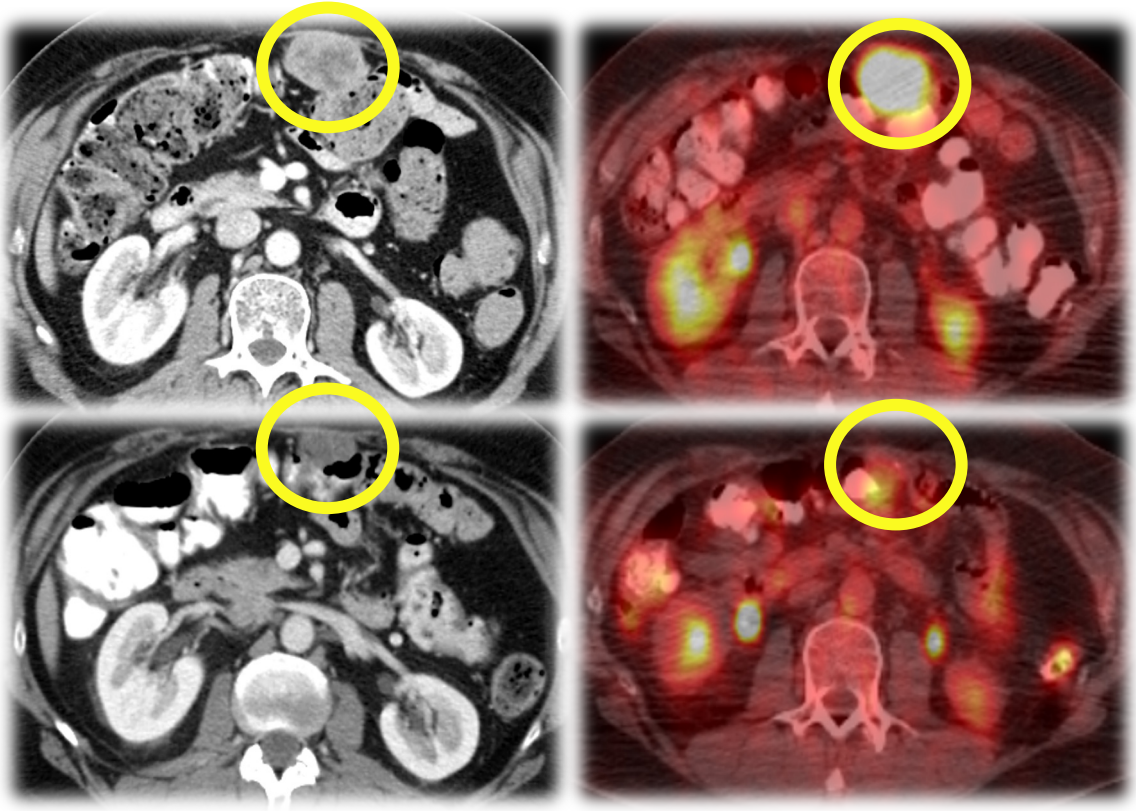
NGS/GIST: PDGFRα EXON 18

CBR = clinical benefit rate
CI = confidence interval
CR = complete response
NE = not evaluable
PD = progressive disease
PR = partial response
SD = stable disease

Heinrich et al. *The Lancet Oncology.* 2020; 21:935-46.

Baseline
4.5x3.2cm
SUV 9.9

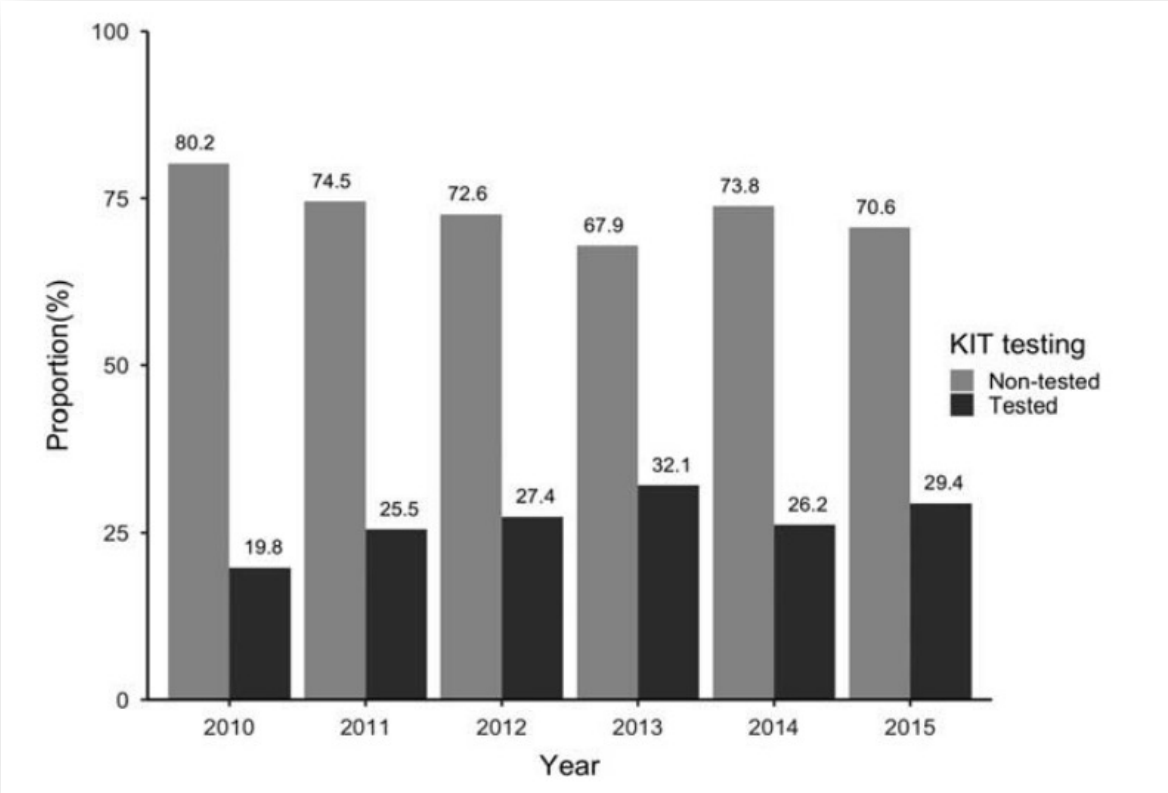
C4D21 of regorafenib
3.0x1.6cm
SUV <3



- Radiographic and metabolic response in pt with **KIT exon 11 and KIT exon 17 resistance mutation** by tissue NGS, treated with next-line **regorafenib**

NGS/GIST: KIT EXON 17 (D820Y) + REGORAFENIB

Serrano, C., Mariño-Enríquez, A., Tao, D.L. et al. *British Journal of Cancer*. 2019.

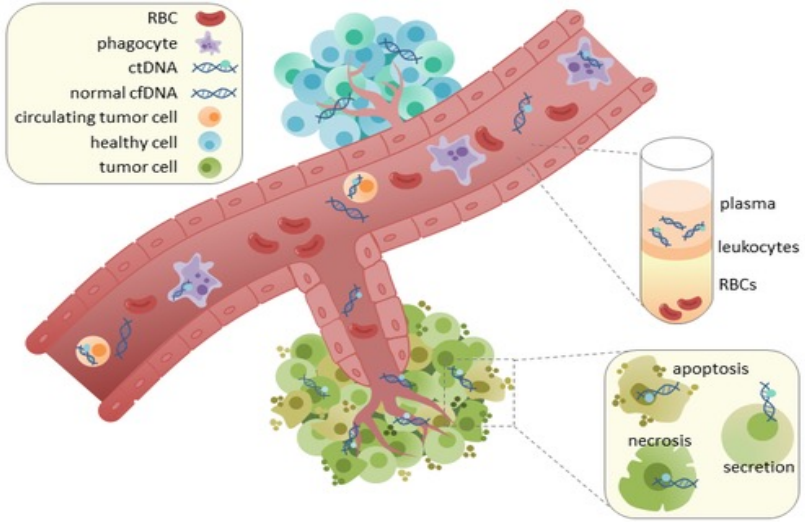


SEER review: **only ~30% of pts** diagnosed with GIST (2010-2015) **underwent mutational analysis**

GIST MUTATION TESTING IN USA

Florindez and Trent. Low Frequency of Mutation Testing in the United States: An Analysis of 3866 GIST Patients. *American Journal of Clinical Oncology*, April 2020. 43 (4), 270-278.

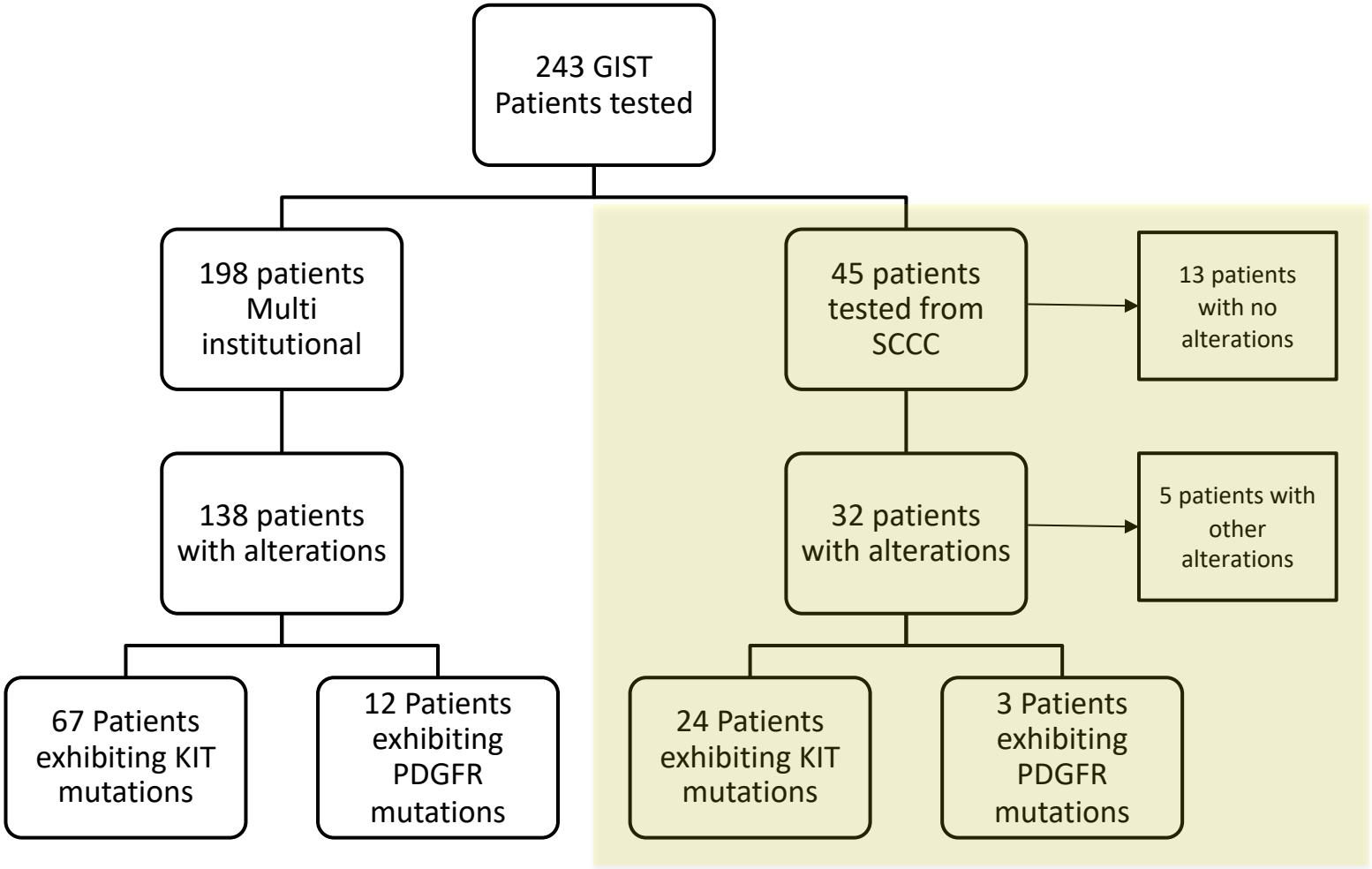
- Provides a **rapid, noninvasive** analysis of current mutations
- Clinical applications in multiple solid tumor cancers
  - emerging predictive value in patients with **metastatic GIST**
- May help define optimal choice of therapy based on **resistance mutations**
  - *KIT* resistance mutations in **GIST**
    - Exon 13
    - Exon 17



INTRODUCTION TO LIQUID BIOPSY

- ctDNA = free, tumor derived DNA in blood (1% of cfDNA)
- cfDNA = free, circulating DNA in blood (of tumor + nontumor origin)

Junaid Arshad, Jon Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.



UTILITY OF ctDNA IN GIST

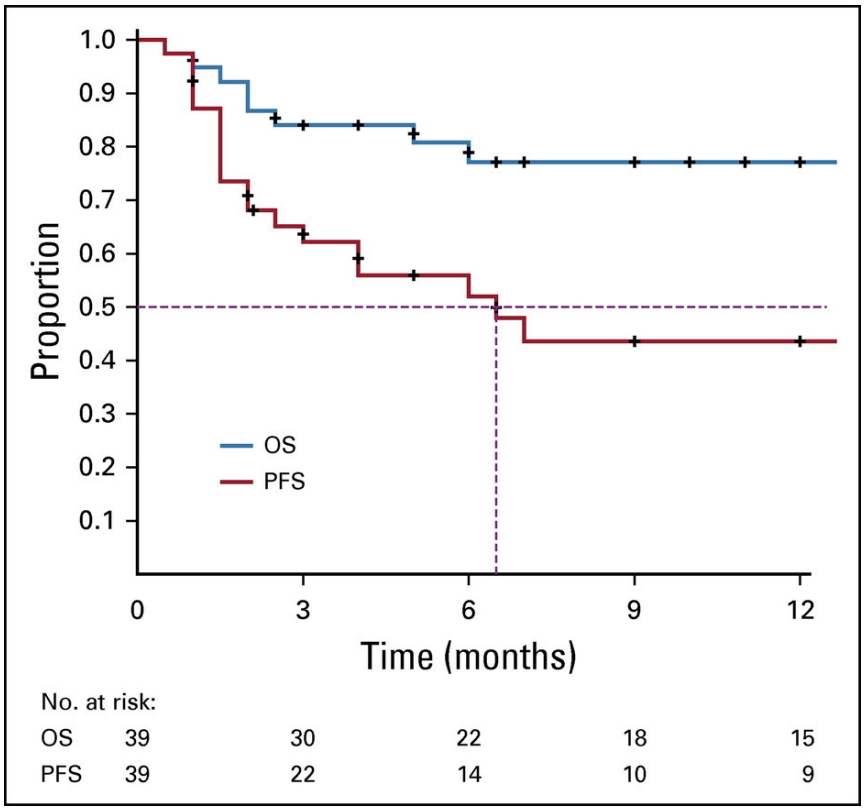
Junaid Arshad, Jon Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.

	ctDNA Mutation+	Tumor FFPE Mutation+	Detection Rate
All Patients	22	36	61%
Primary Tumor	0	6	0%
Metastatic Low Volume	1	6	16%
Metastatic and Responding	0	3	0%
Metastatic, Large, and Progressive	21	21	100%

UTILITY OF ctDNA IN GIST

Junaid Arshad, Jon Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.

* Large = sum of 3 largest lesions $\geq$ 10 cm



12 months from ctDNA testing (*n* = 39):

OS = 79.5%; CI 0.66-0.92
PFS = 46.2%; CI 0.32-0.65

UTILITY OF ctDNA IN GIST

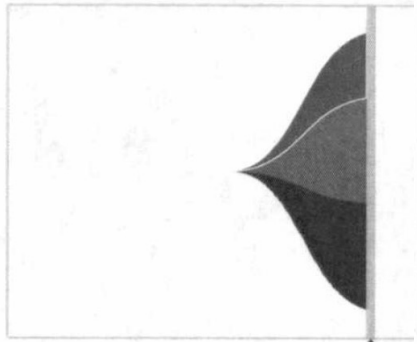
Arshad, Trent, et al. *JCO Precision Oncology* no. 4 (2020) 66-73.

55yo Caucasian male with **stage IV gastric GIST** (*KIT* exon 11 W557-558del), **liver and intraabdominal metastases**

Progressive disease w/

1. Imatinib
2. Sunitinib
3. Regorafenib

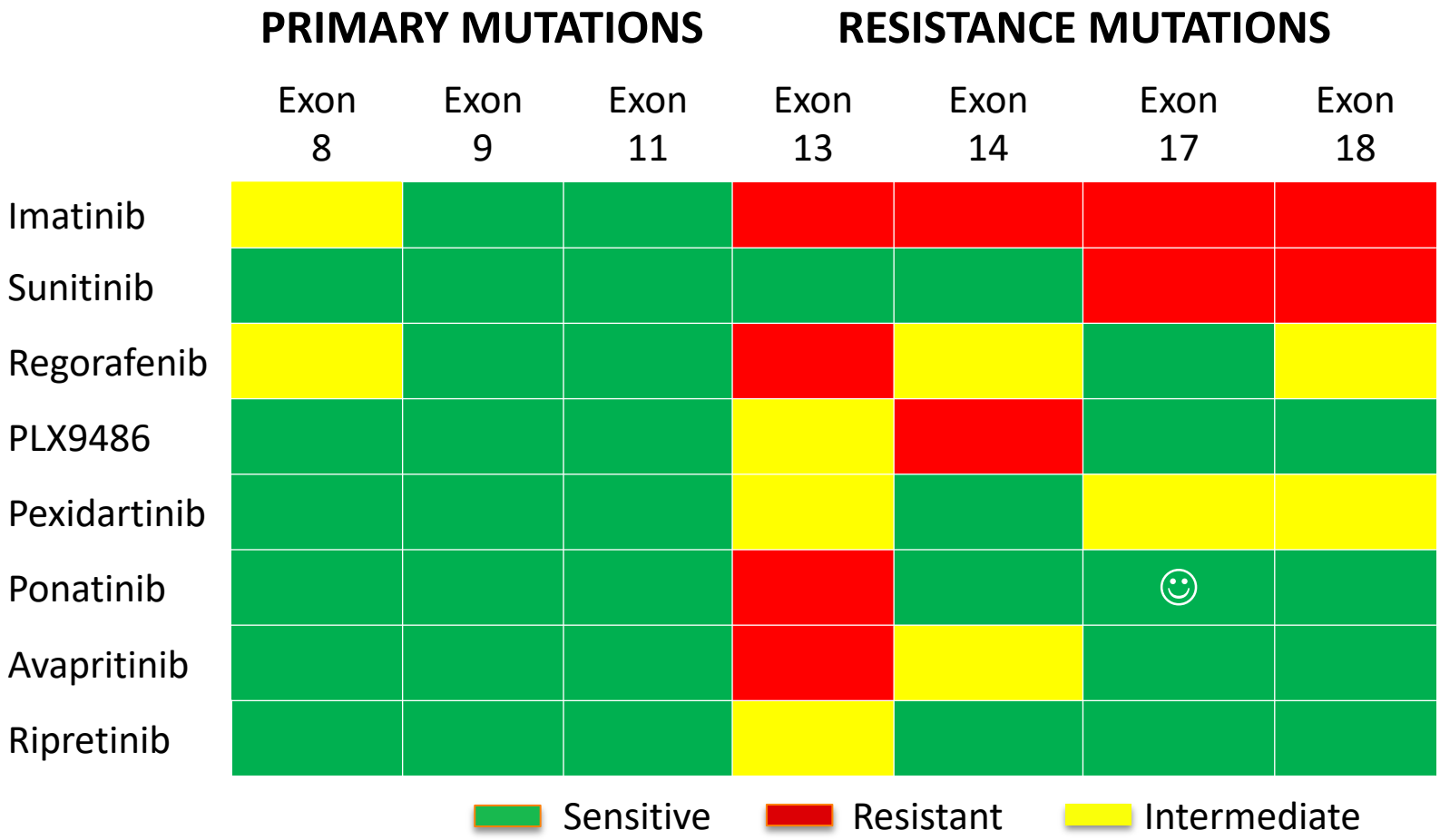
→ Referred to hospice → Liquid biopsy via ctDNA



Alteration		% cfDNA or Amplification	FDA Approved in Indication *see page 3*	Available for Use in Other Indications *see page 3*	Clinical Drug Trials *see page 9*
Relevant for Therapy Selection					
PIK3CA	*G1049S*	0.2	None	None	Trials Available Nearby
KIT	***Y823D***	0.2	Regorafenib, Sunitinib Lack of Response: Imatinib	Axitinib, Cabozantinib, Dasatinib, Lenvatinib, Nilotinib, More drugs available	Trials Available Nearby
KIT	*W557_K558del (Exon 11 Deletion)*	0.1	Regorafenib, Sunitinib	Axitinib, Cabozantinib, Dasatinib, Lenvatinib, Nilotinib, More drugs available	Trials Available Nearby

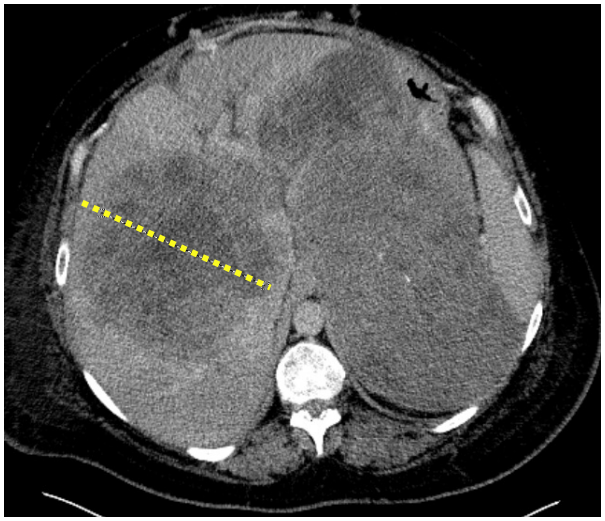
CASE PRESENTATION

Heinrich et al. JCO 21.23 (2003): 4342-4349.

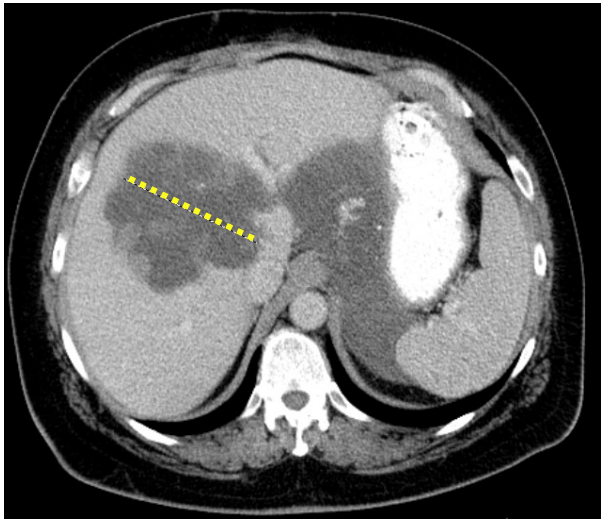


KIT SECONDARY MUTATIONS

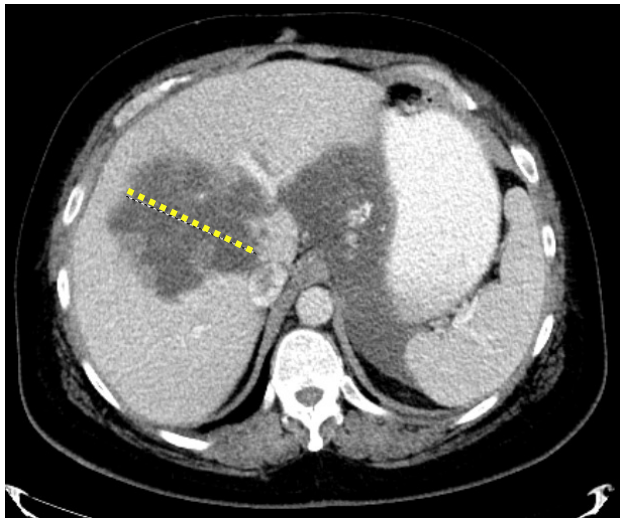
Junaid Arshad, Jonathan C. Trent. *JCO Precision Oncology* 2020.
Trent, CTOS 2017. Serrano BJC 2018.
Gramza et al, Clinical Cancer Research 15:7510, 2009
Heinrich et al, ASCO 2013 Poster/Abstract 10509



*Baseline; **before** ponatinib*



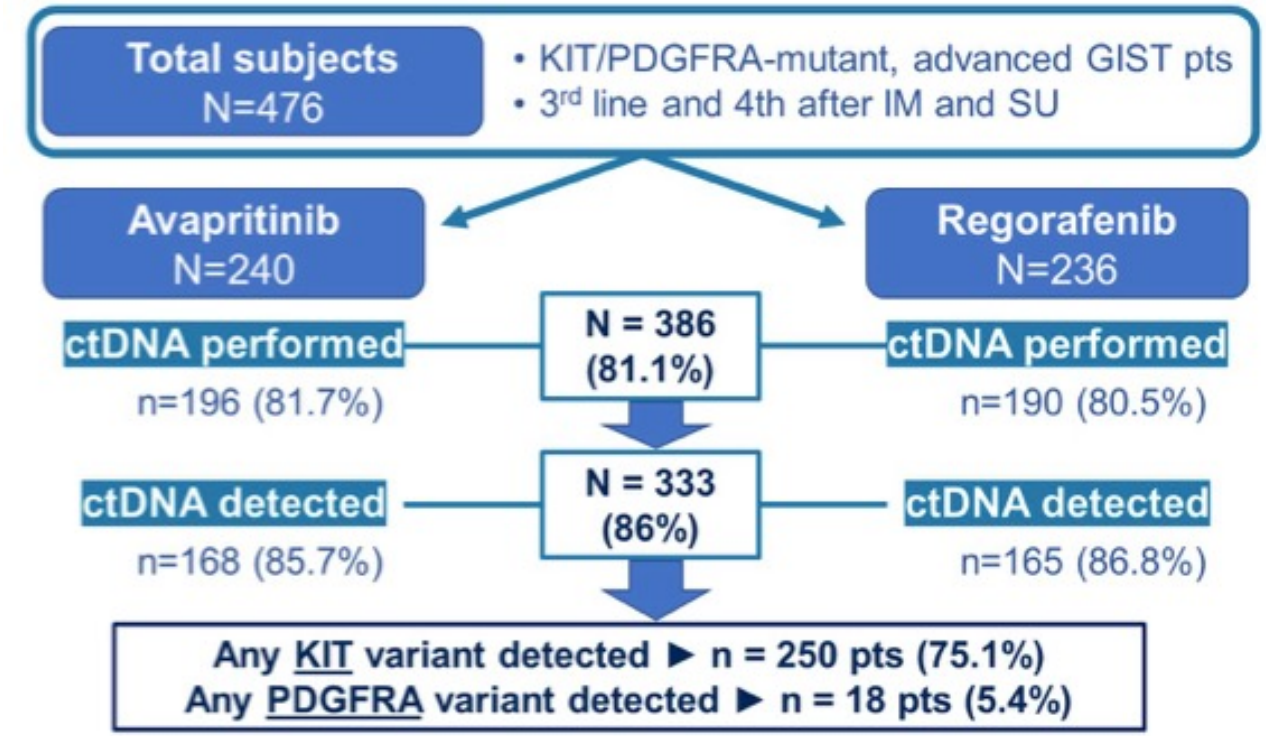
*After **6 months** of ponatinib*



*After **12 months** of ponatinib*

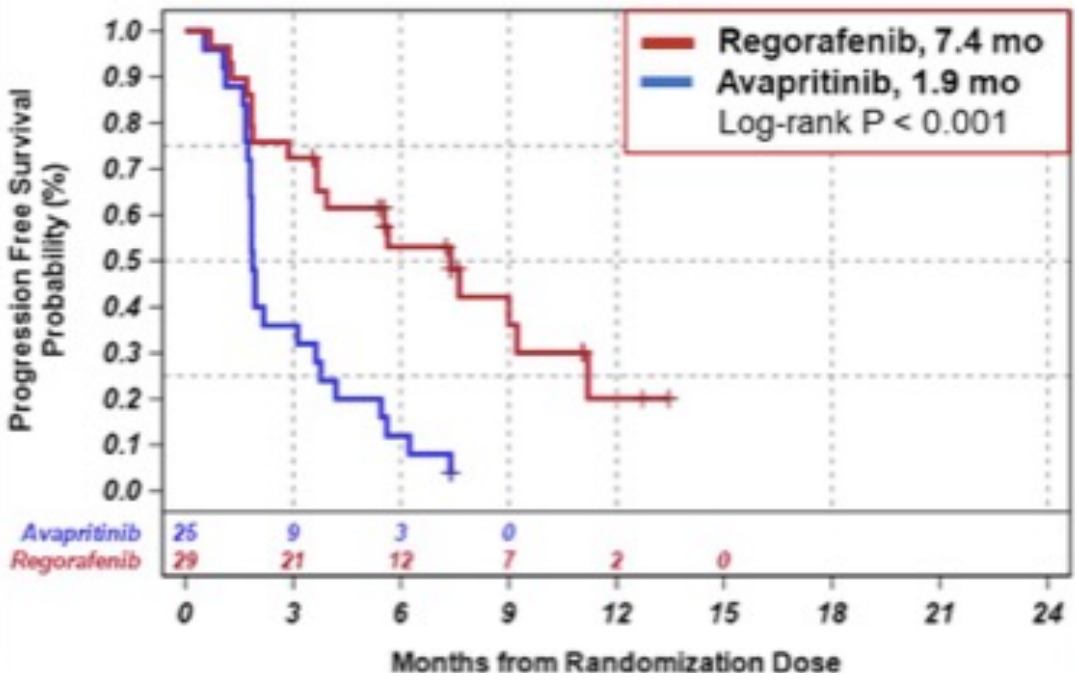
DISEASE RESPONSE

ctDNA analyses in phase III VOYAGER trial: KIT mutational landscape and outcomes in pts with advanced GIST



VOYAGER Trial

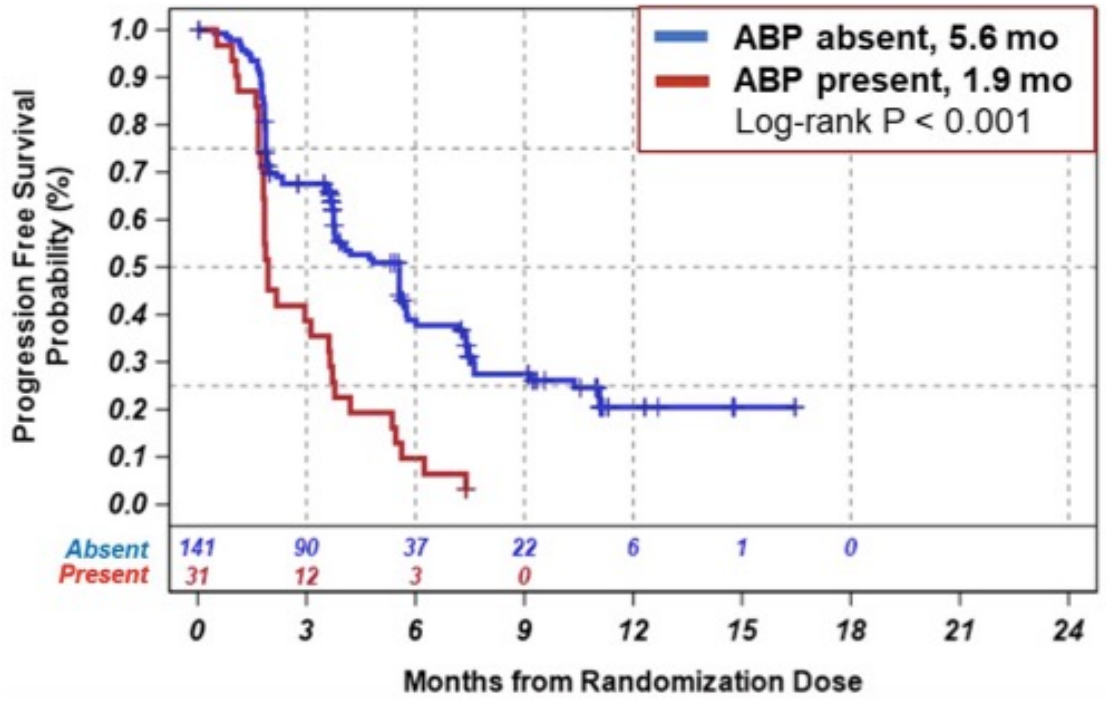
Serrano et al. ASCO 2022.



Patients with **Kit exon 13 resistance mutations** are progression free longer when treated with **regorafenib** over avapritinib

VOYAGER Trial

Serrano et al. ASCO 2022.



Patients without **KIT exon 13 resistance mutation** remain progression free on **avapritinib** compared to regorafenib

VOYAGER Trial

Serrano et al. ASCO 2022.

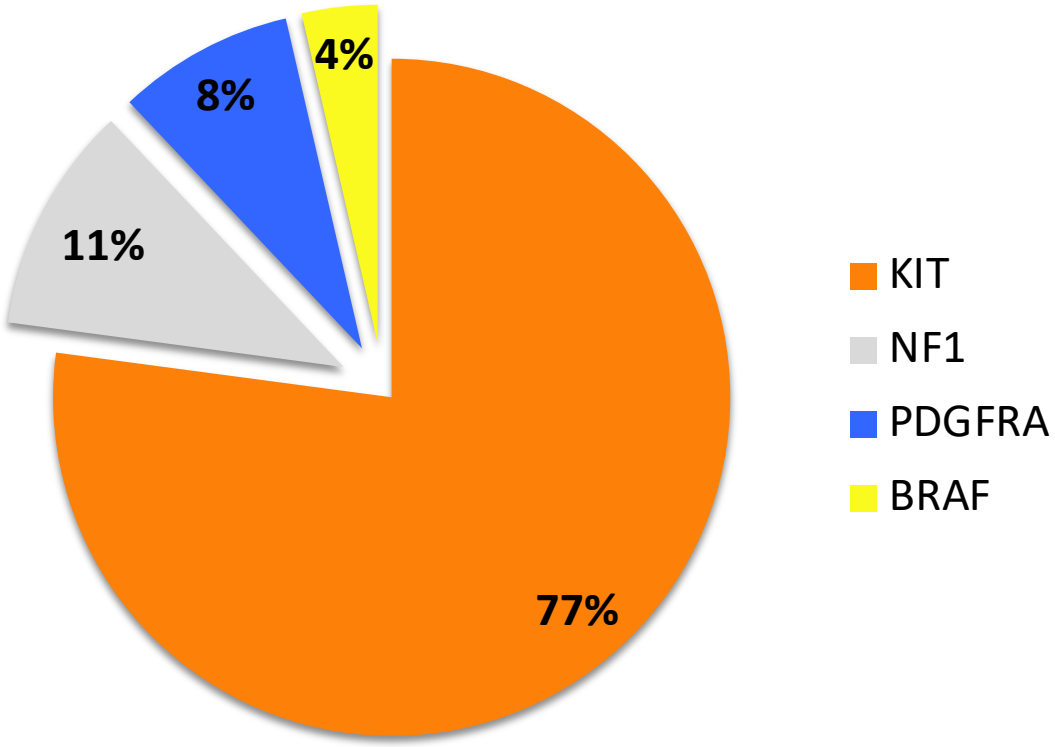
ctDNA AND *KIT* RESISTANCE MUTATIONS

KIT Resistance Mutations Identified by Circulating Tumor DNA and Treatment Outcomes in Advanced Gastrointestinal Stromal Tumor.
*Poster discussion session at **ASCO 2022.***

Steve Bialick, DO, MS
Hematology/Oncology Fellow, PGY6
Sylvester Comprehensive Cancer Center

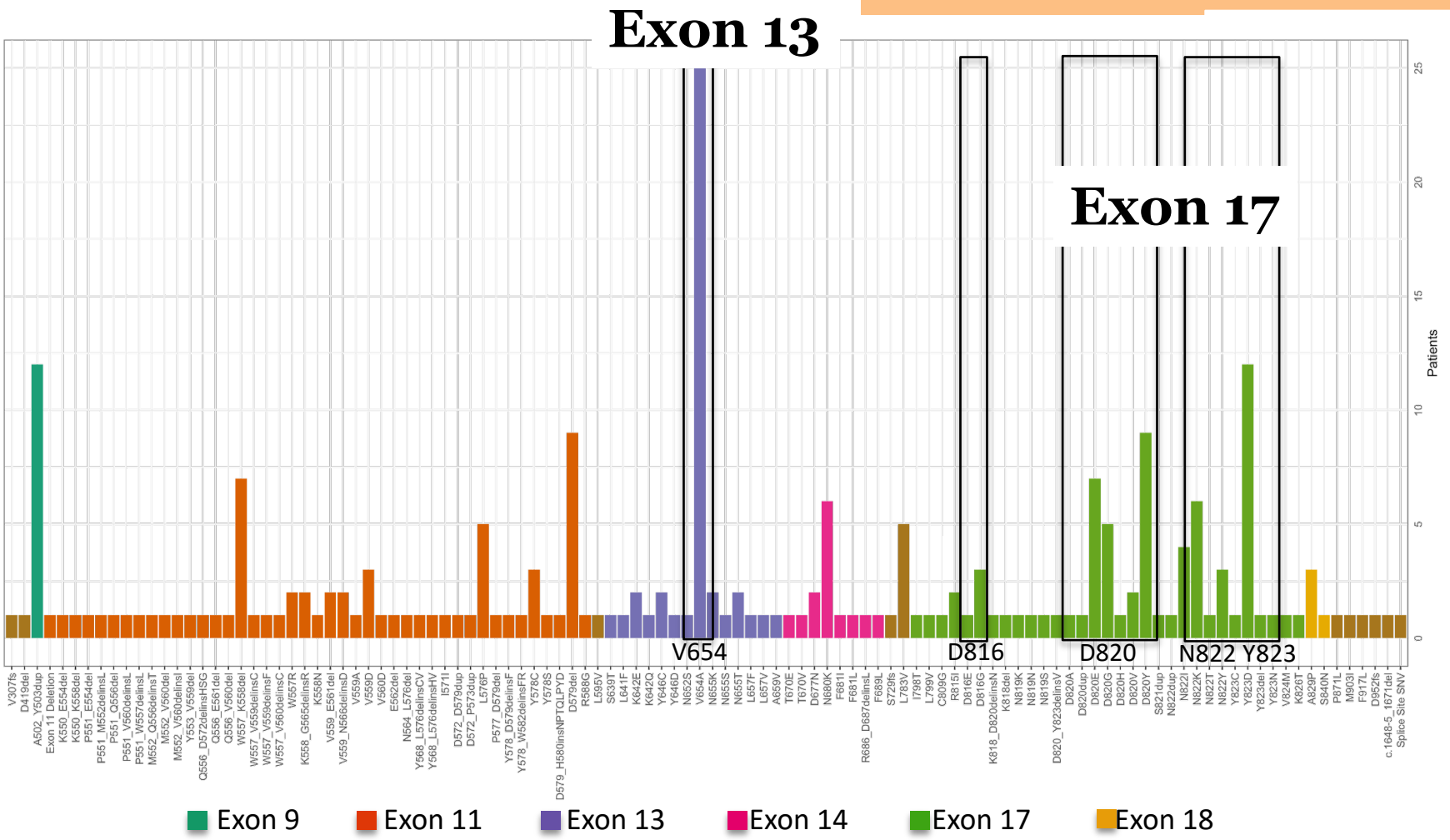
- *KIT*-mutant GIST patients benefit from first-line (1L) imatinib
- ***KIT*-resistance mutations** confer **differential sensitivity** to subsequent TKI

BACKGROUND

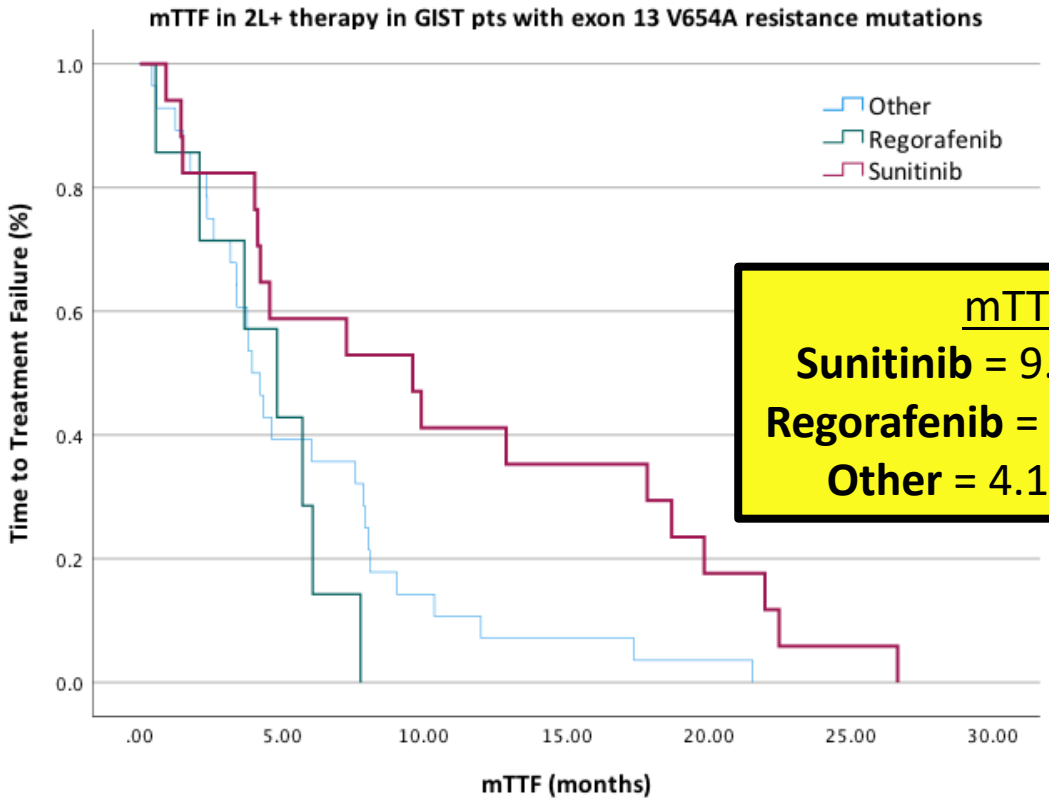


- Patients with common driver mutation (n=83)
- Patients with *KIT* mutation (n=64)

COMMON GIST DRIVER ONCOGENES BY ctDNA



SPECIFIC *KIT* ALTERATIONS DETECTED



mTTF
Sunitinib = 9.6 months
Regorafenib = 4.8 months
Other = 4.1 months

HR = 0.677
CI: 0.49-0.93
p=0.01

Patients with Kit exon 13 resistance mutations do twice as well on sunitinib then regorafenib

2L+ mTTF *KIT* EXON 13 (V654A) PATIENTS

CONCLUSIONS

- ctDNA is a noninvasive tool for **detecting driver and resistance mutations** in pts with advanced GIST.
- GIST pts with ctDNA is an emerging technology which may impact therapeutic decision-making
- ctDNA-guided therapy warrants **evaluation in a prospective clinical trial:** Phase II Study of ctDNA-guided Sunitinib and Regorafenib Therapy for Gastrointestinal Stromal Tumor (GIST)

Medical Oncology

- Jon Trent
- Gina D'Amato
- Emily Jonczak
- Aditi Dhir (ped)

Nurse Practitioner

- Morgan Smith
- Solange Sierra
- Alisette Naveda

Pathology

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- Elizabeth Montgomery
- Daniel Cassidy
- Jay-Lou Velez Torres

Radiology

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- Francesco Alessandrino

Orthopedic Oncology

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- Tom Temple
- Sheila Conway
- Frank Eismont
- Juan Pretell
- Mo Al Maaieh

Surgical Oncology

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- Alan Livingstone
- Neha Goel
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Radiation Therapy

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- **Steve Bialick**
- Philippos Costa
- Andrea Espejo-Freire

SYLVESTER TEAM SARCOMA

Thank You!

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