CHAMPIONING MEDICALLY INTEGRATED ONCOLOGY:

Celebrating a Decade of Impact

2025 NCODA INTERNATIONAL FALL SUMMIT

Get the GIST of Precision Medicine

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SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

OBJECTIVES

1. Describe the molecular subtypes of GIST and the role of mutation testing in guiding treatment selection.

2. Discuss the utility of circulating tumor DNA (ctDNA) in detecting resistance mutations and informing sequencing of TKIs.

3. Recall strategies to optimize treatment for patients with GIST across different mutational profiles.

DISCLOSURES

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty and planners of this CE activity:

- **Jon Trent, MD, PhD**
  - Deciphera, Bayer, Daiichi Sankyo, Eisai, IDRx

There are no relevant conflicts of interest to disclose for this presentation for the following planners and speakers:

- **Nikki West, PharmD, BCOP**
- **Ginger Blackmon, PharmD**
- **Tahsin Imam, PharmD**

QUESTION 1

How familiar are you with the use of circulating tumor DNA (ctDNA) in guiding therapy for gastrointestinal stromal tumors (GIST)?

a. Very familiar – I routinely apply ctDNA findings in practice
b. Somewhat familiar – I understand the concept but rarely use it
c. Not familiar – This is a new topic for me

GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- High frequency of metastatic disease
- Gene mutations drive phenotype and therapy
- Metastatic disease treated with tyrosine kinase inhibitors (TKIs)

Parekh AD et al. *Am J Clin Oncol*. 2020;43(4):270-278.

KIT Receptor Structure

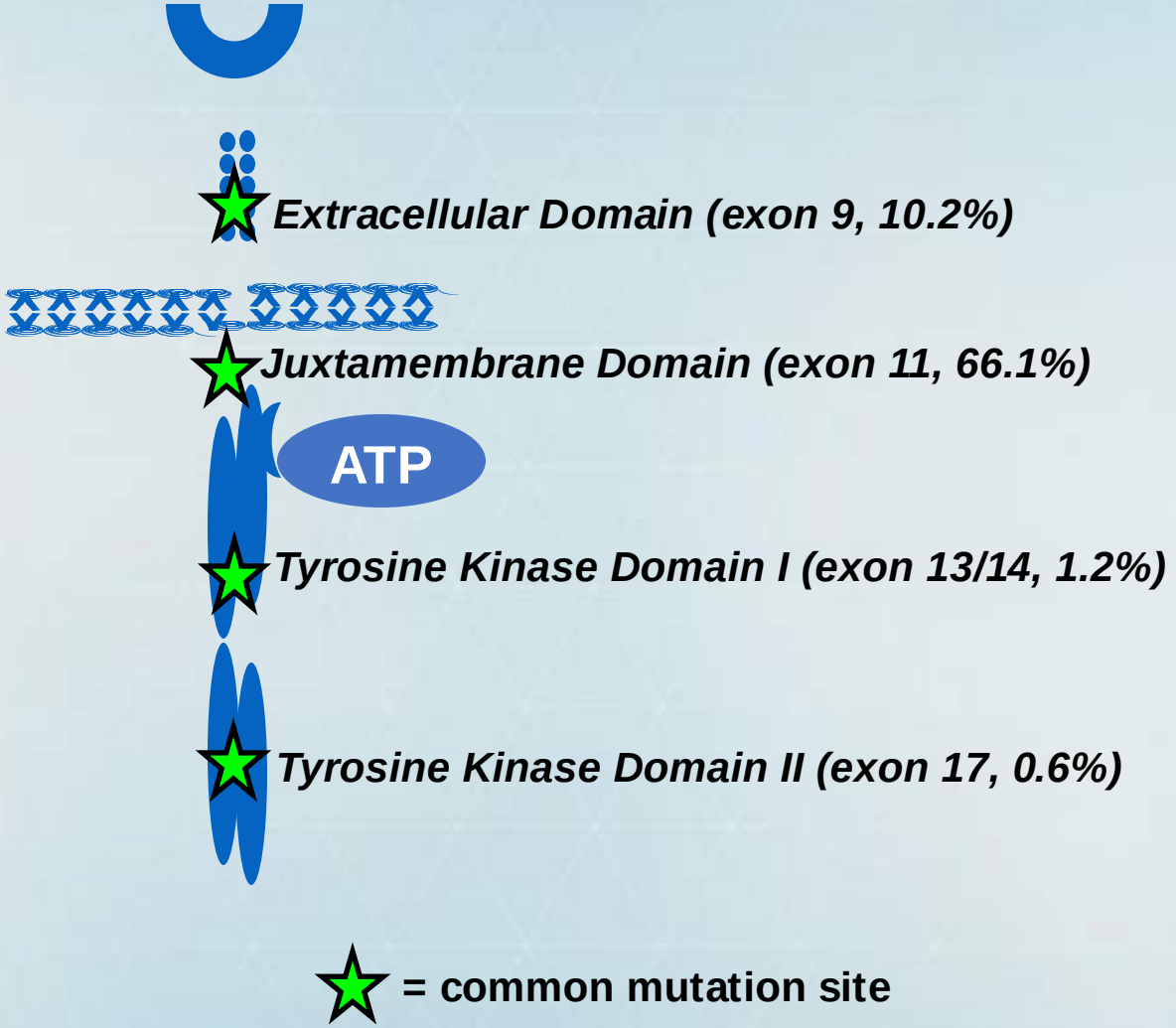


Image credit: Jonathan C. Trent, MD, PhD

KIT Receptor Phenotype

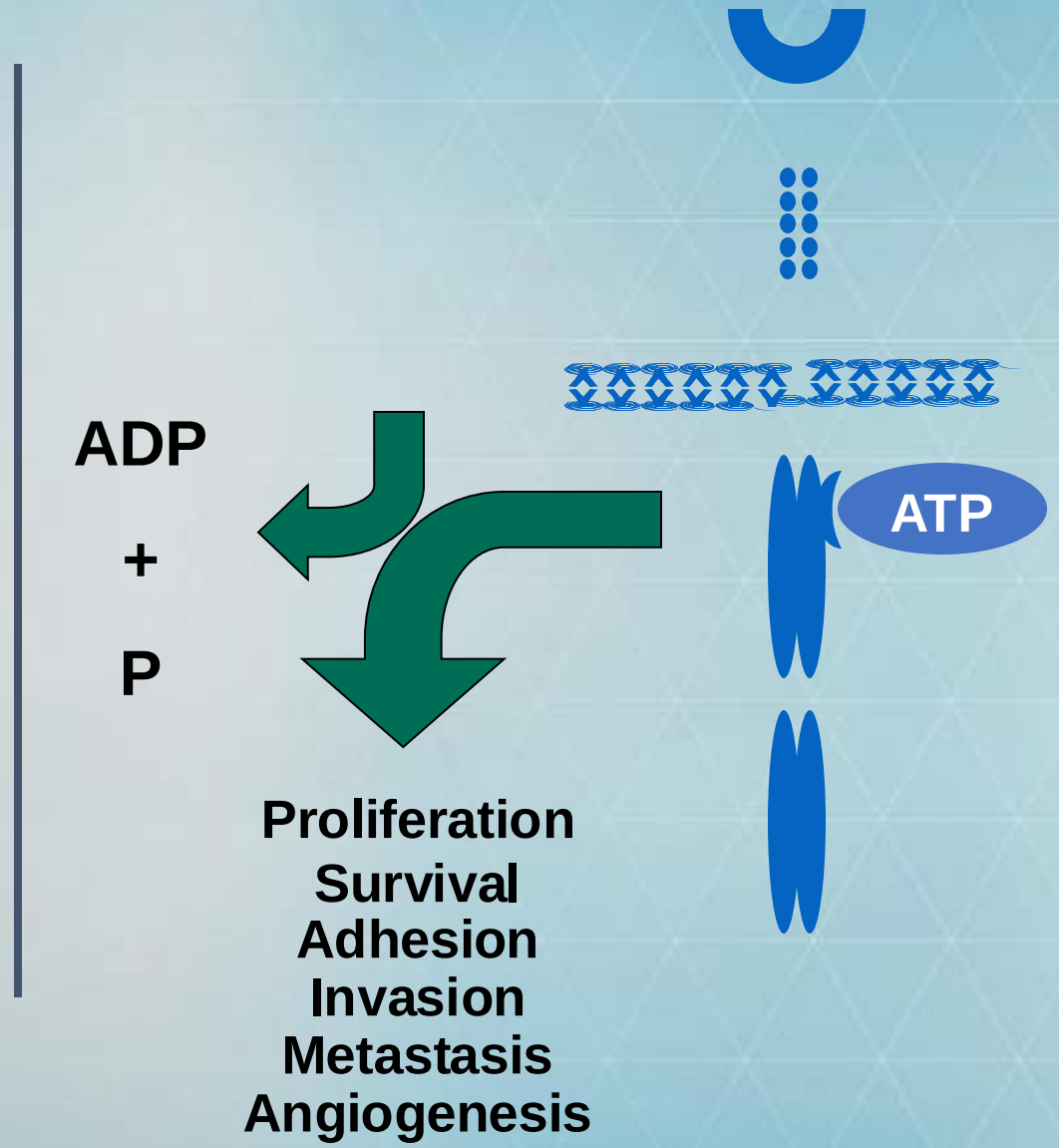


Image credit: Jonathan C. Trent, MD, PhD

KIT Receptor Phenotype

Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imatinib contact point

Image credit: Jonathan C. Trent, MD, PhD

GIST Overview (Continued)

Metastatic disease treated with TKIs

- Imatinib (PFS = 24 months)
- Sunitinib (PFS = 6 months)
- Regorafenib (PFS = 5 months)
- Ripretinib (PFS = 6.3 months)
- Avapritinib (PFS = 3.7 months)
- Avapritinib PDGFR (PFS = NR)

Parekh AD et al. *Am J Clin Oncol*. 2020;43(4):270-278. doi:10.1097/COC.0000000000000659

GIST Subtypes

KIT exon 11

KIT exon 9

KIT resistance mutations

Exon 13 (ATP binding site)

Exon 17 (A-loop)

PDGFR D842V

SDH deficiency

Raf V600E

NF-1, Ras

PI3K

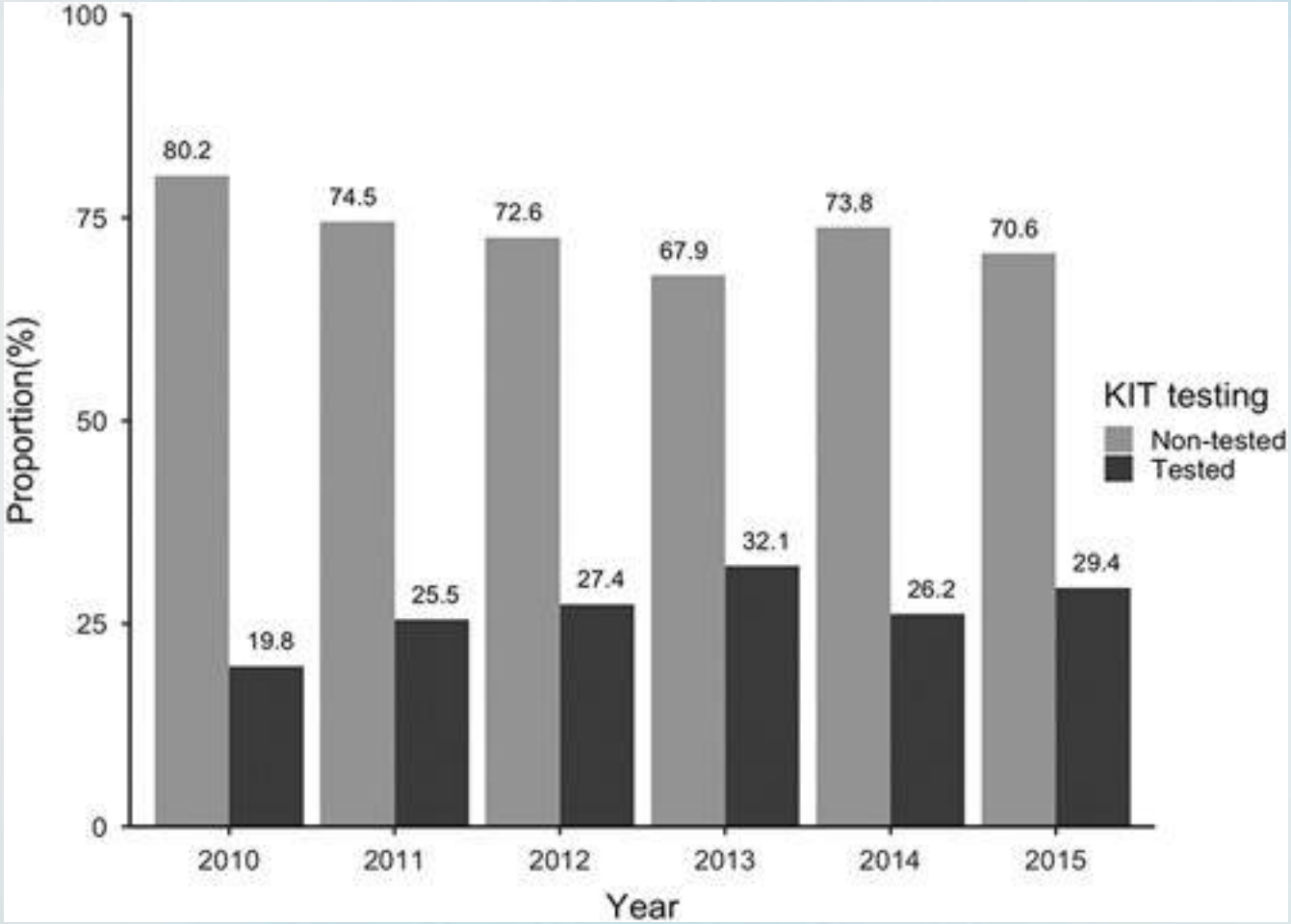
IGF-1R expressing

TRK fusion

National Comprehensive Cancer Network (NCCN). *Gastrointestinal Stromal Tumors (GIST).*

Casali PG, Blay J-Y, Abecassis N, et al; ESMO Guidelines Committee, EURACAN, GENTURIS. Gastrointestinal stromal tumours: ESMO–EURACAN–GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(1):20-33. doi:10.1016/j.annonc.2021.09.005.

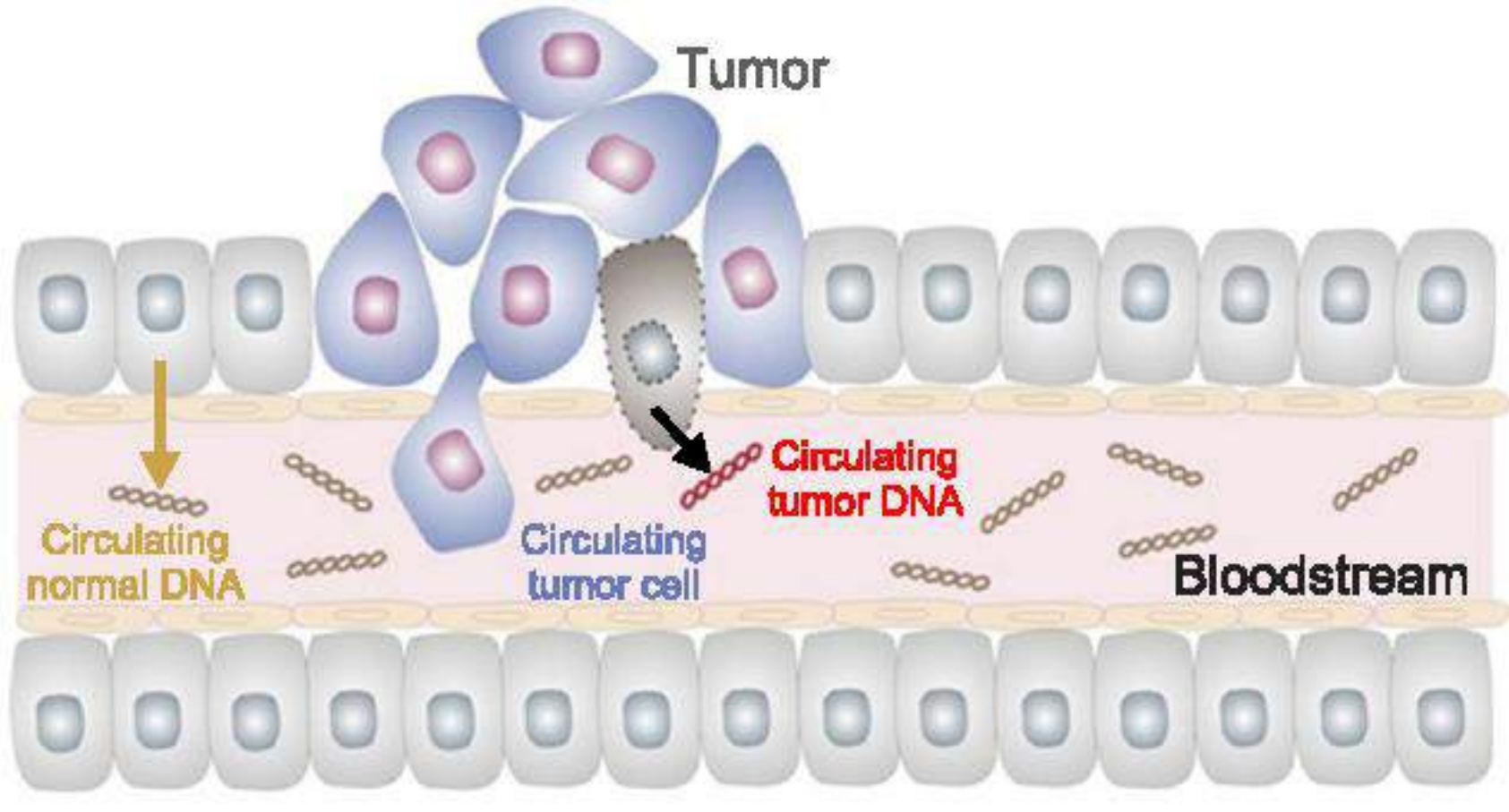
GIST Mutation Testing in US



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

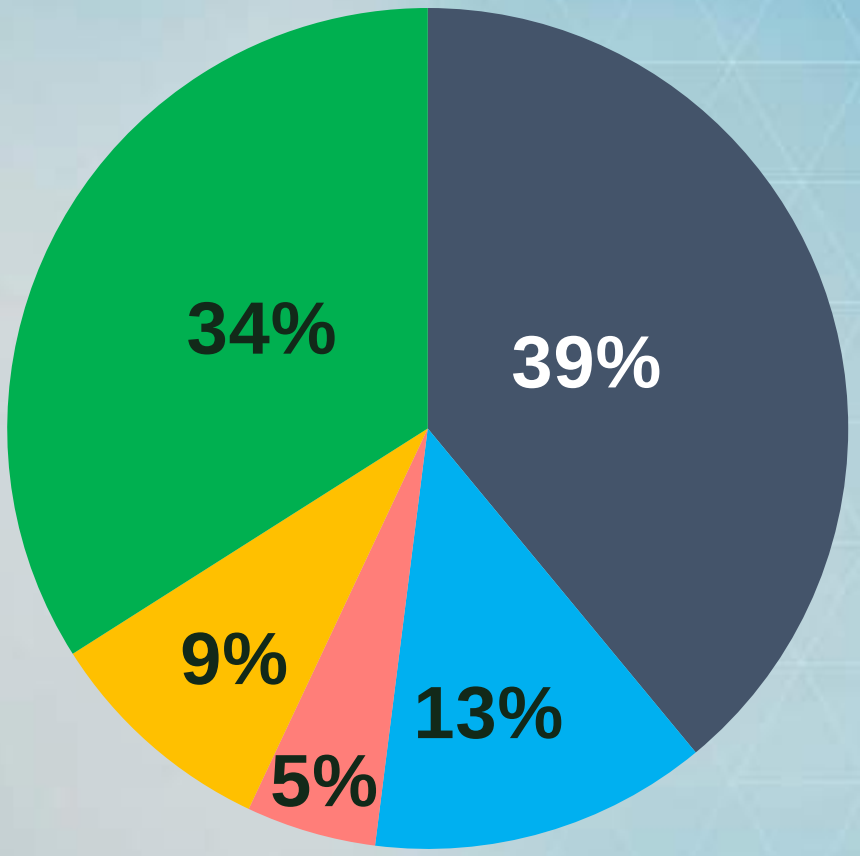
Circulating Tumor DNA (ctDNA)

Mutation Testing From Blood (Liquid Biopsy)



Nurwidya F et al. *Oncol Rev.* 2018.
Bauer S et al. *J Clin Oncol.* 2015.
Serrano C et al. *Br J Cancer.* 2018.

Distribution of Primary Mutations (%)

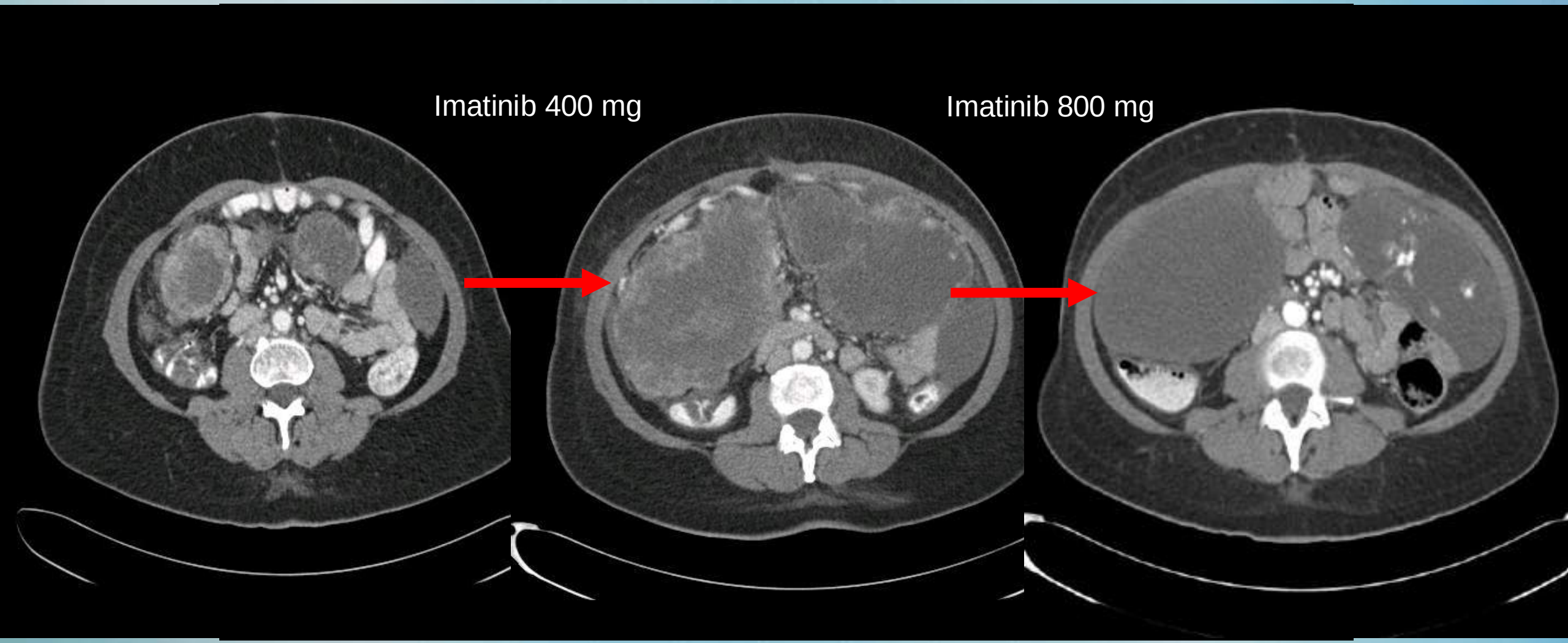


- Patients with mutation (n=162)
- KIT or PDGFR mutations (N=106)
- Not KIT/PDGFR (N=56)

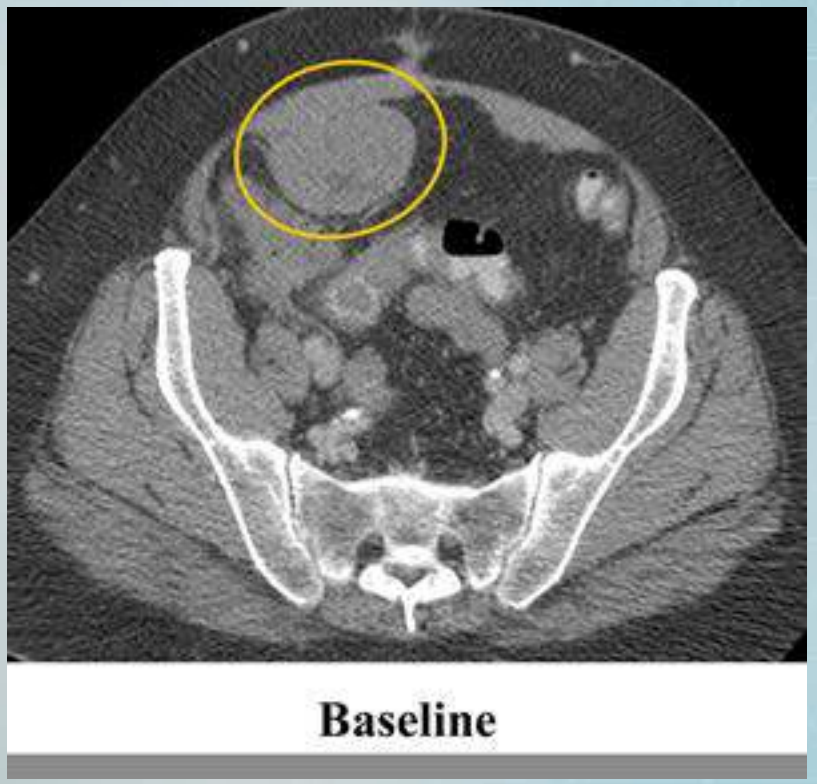
Kit exon 11 KIT exon 9 KIT other

Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

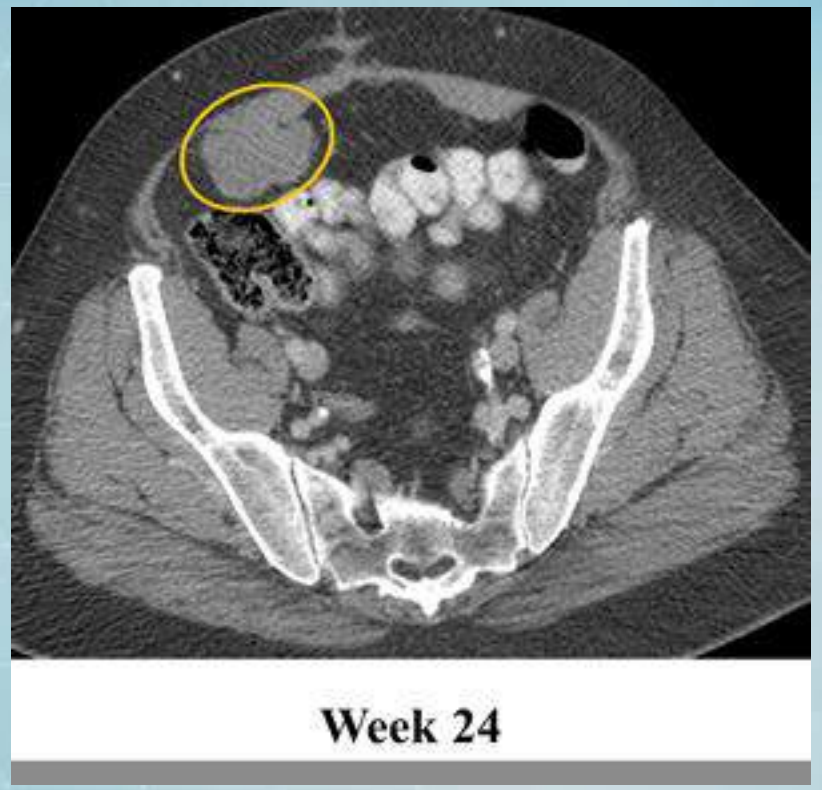
GIST Patient Initial Therapy
KIT Exon 9 Mutation



GIST Patient Initial Therapy
RAF V600E Mutation



Baseline

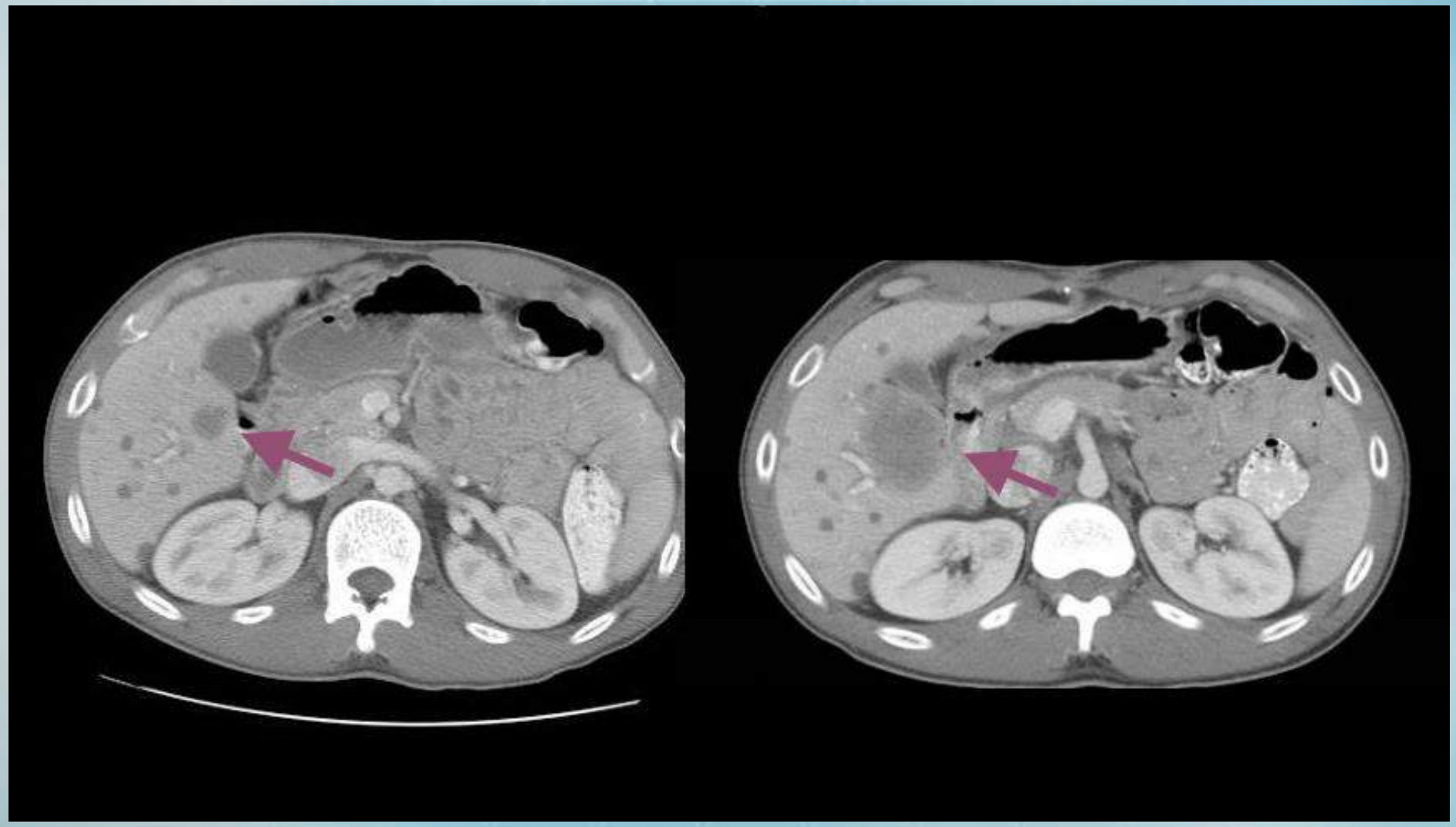


Week 24

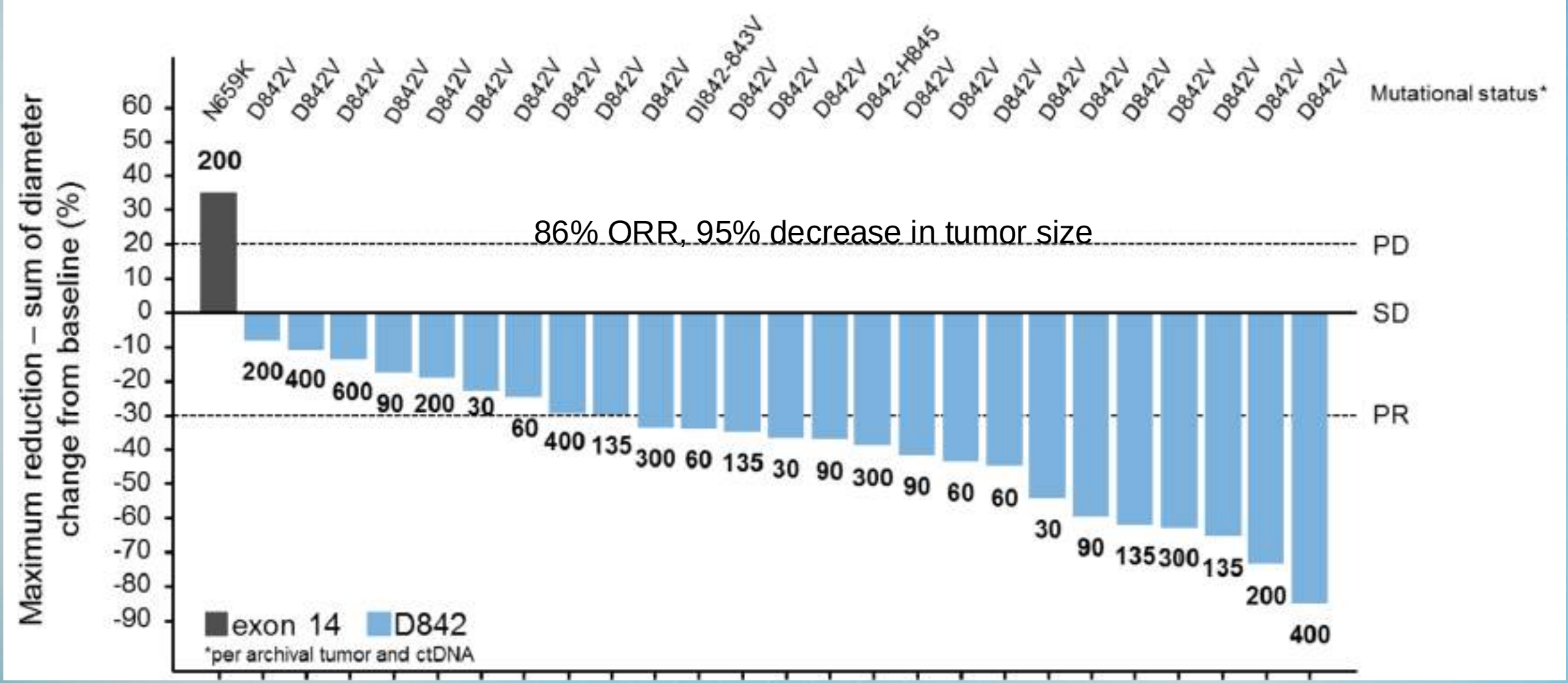
Treatment with RAF inhibitor Vemurafenib

Falchook, Trent, Heinrich. Oncotarget. 2013 Feb;4(2):310-5.

GIST Patient Initial Therapy
PDGFR D842V Mutation



Avapritinib
PDGFR D842V Mutant GIST

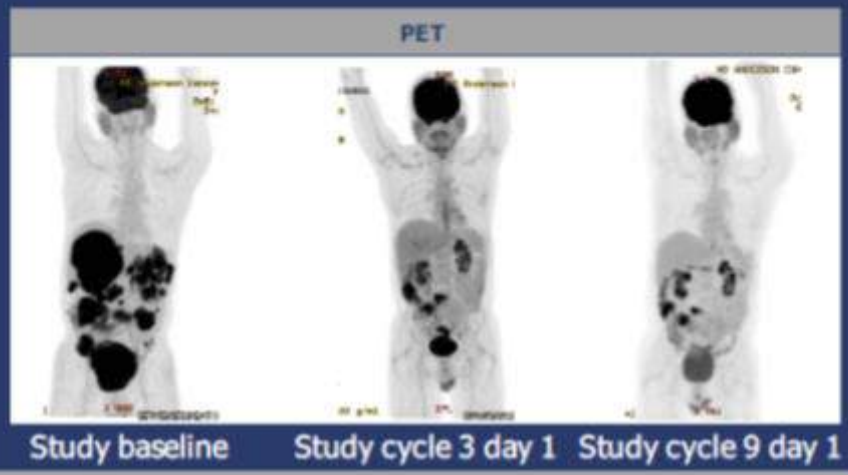


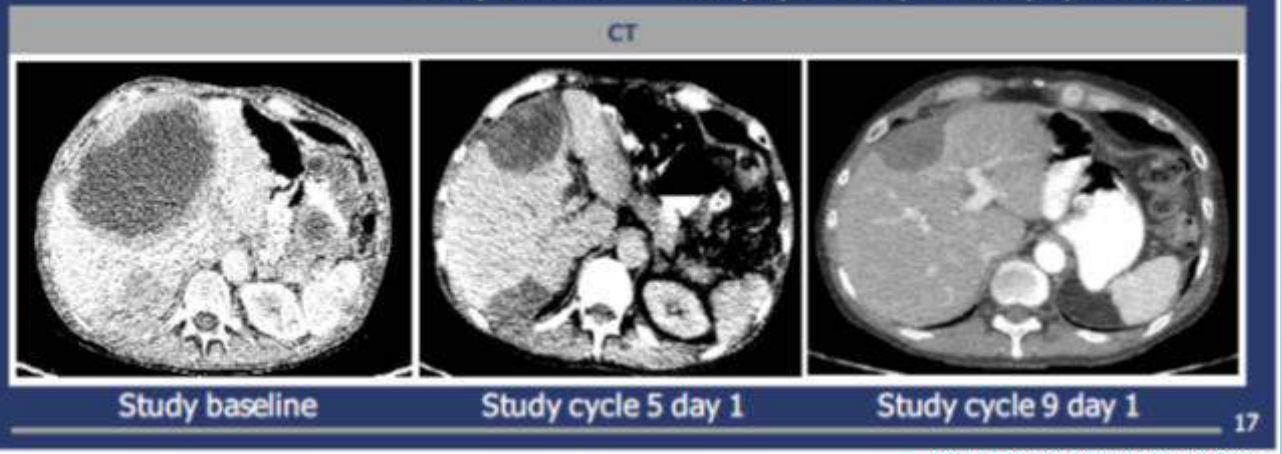
Heinrich, Trent, et al. Lancet Oncology 2020.

GIST With TRK Fusion

Patient #2:
ETV6-NTRK3 fusion

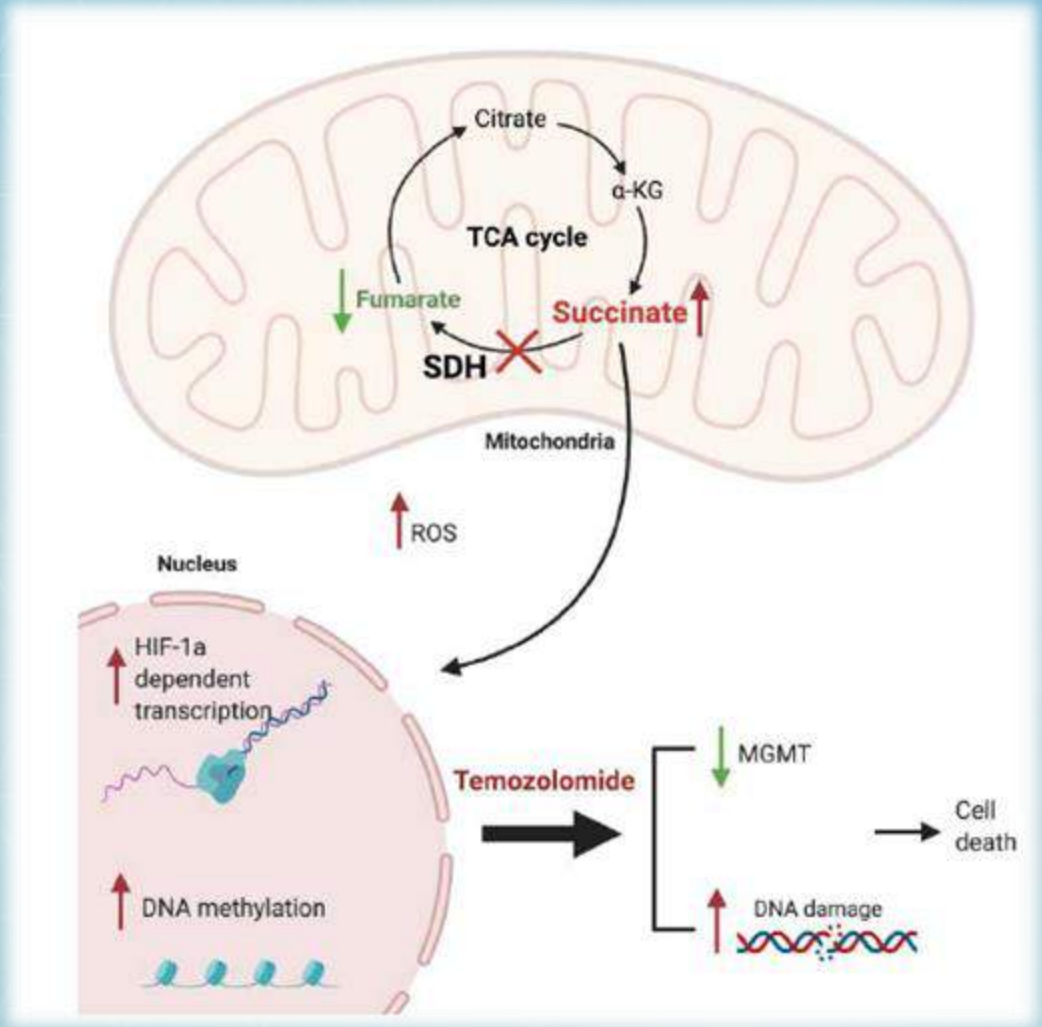
Larotrectinib
Entrectenib





Hong DS et al. *SEC Form 8-K*, Ex. 99.2. 2016. Available at: https://www.sec.gov/Archives/edgar/data/1581720/000110465916111952/a16-8544_1ex99d2.htm

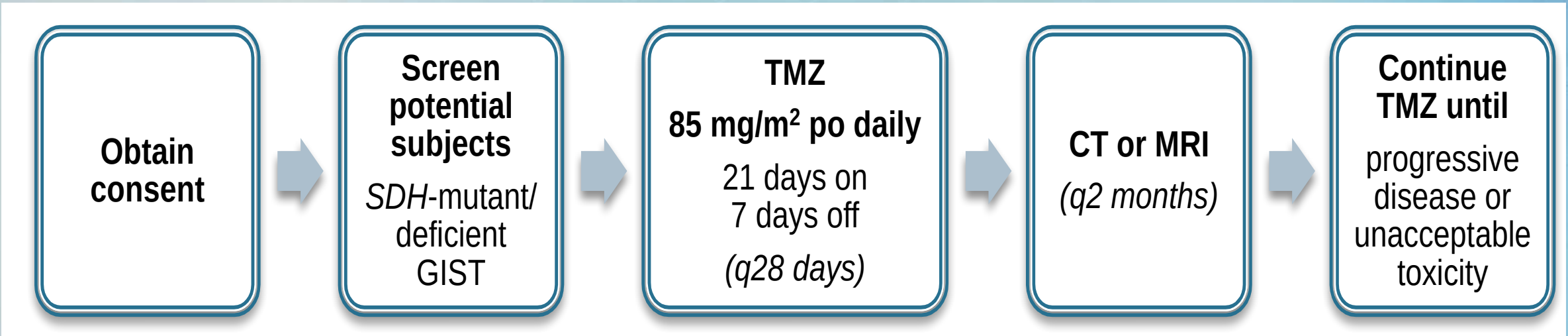
Temozolomide is effective against SDH-def GIST



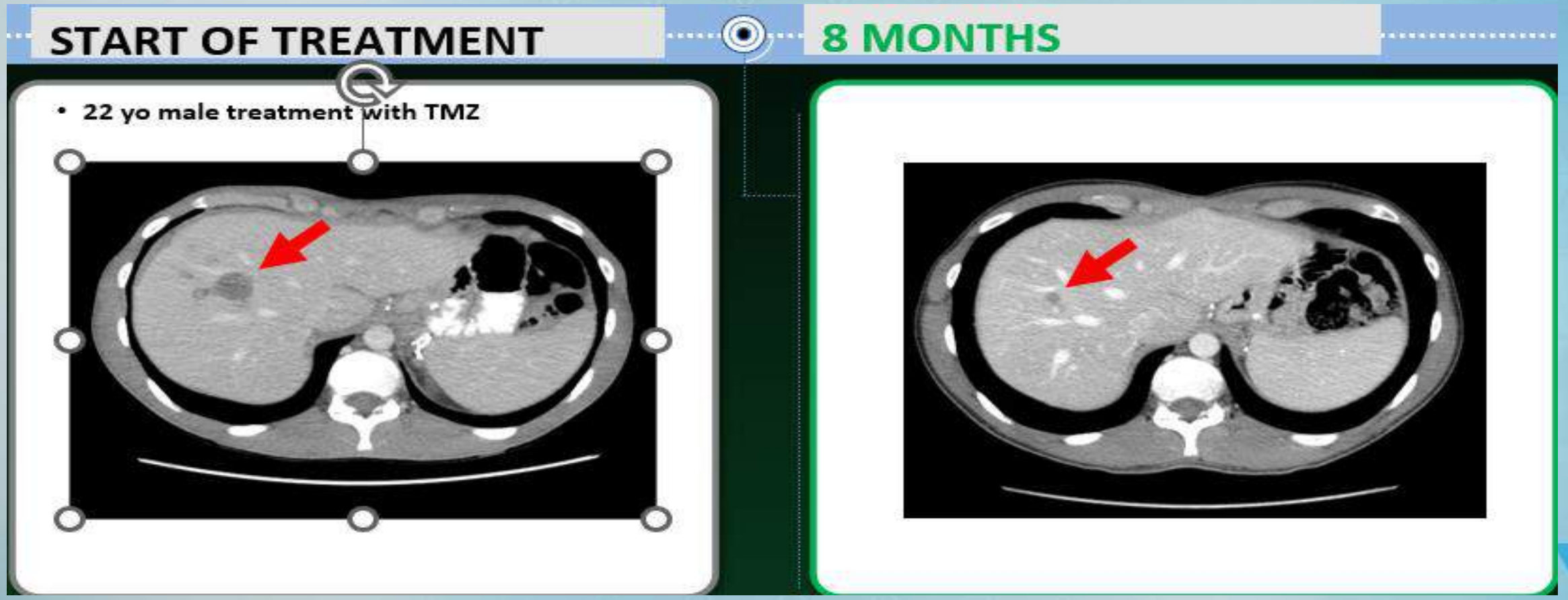
Giger OT, ten Hoopen R, Shorthouse D, et al. Preferential MGMT hypermethylation in SDH-deficient wild-type gastrointestinal stromal tumours. *J Clin Pathol.* 2024;77(1):34-39.

Selak MA, Armour SM, MacKenzie ED, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF-α prolyl hydroxylase. *Cancer Cell.* 2005;7(1):77-85.

Study Design



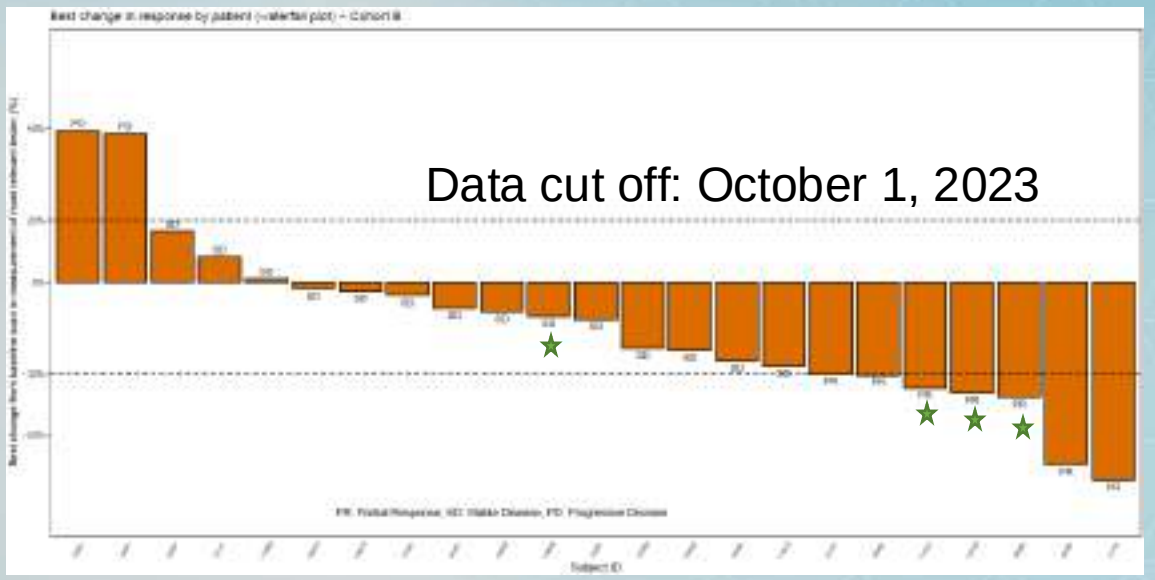
Temozolomide Patient with *SDHB* R90* GIST (Progression on 3 TKI therapies)



Yebra, Bhargava, et al, *Clinical Cancer Research*, July 2021

Rogoratinib for Patients with SDH Deficient GIST

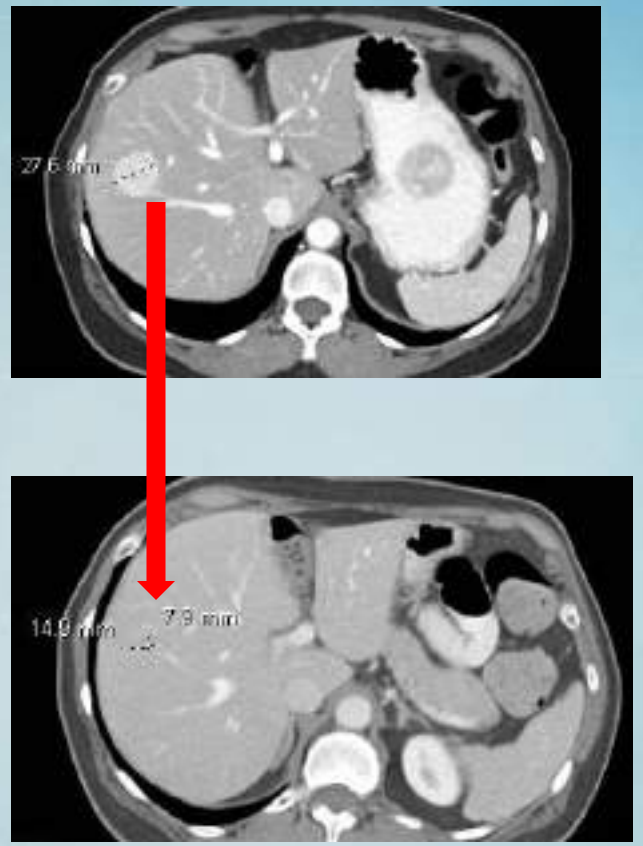
Efficacy



★ Unconfirmed response

Best Overall Response (n= 23)
PR: 7 (3 unconfirmed)
SD: 14 (1 unconfirmed)

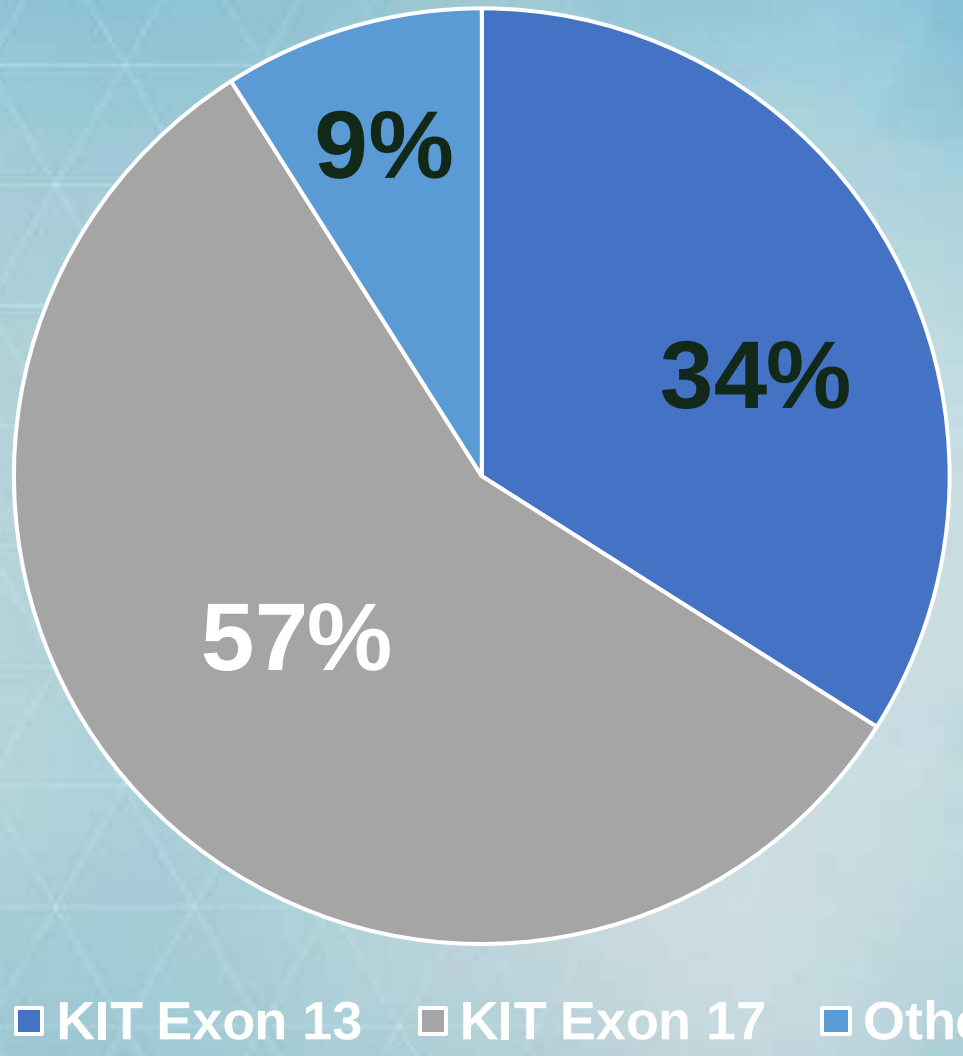
4 of 23 Partial Response = 17% PR



Priscilla Merriam, MD; CTOS 2024

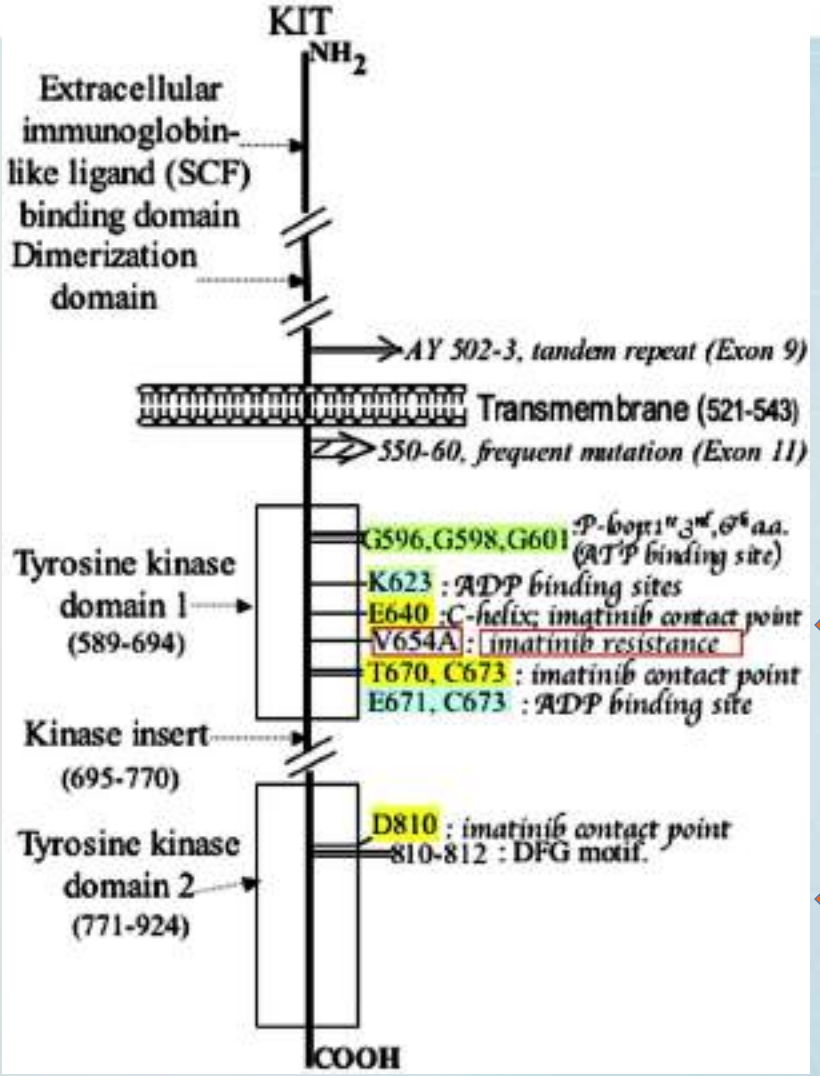
Resistance Mutations (%)

- Patients with KIT or PDGFR mutation (n=106)
- Other: Ras, NF-1, PI3K, TSC



Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

Secondary Mutations in KIT



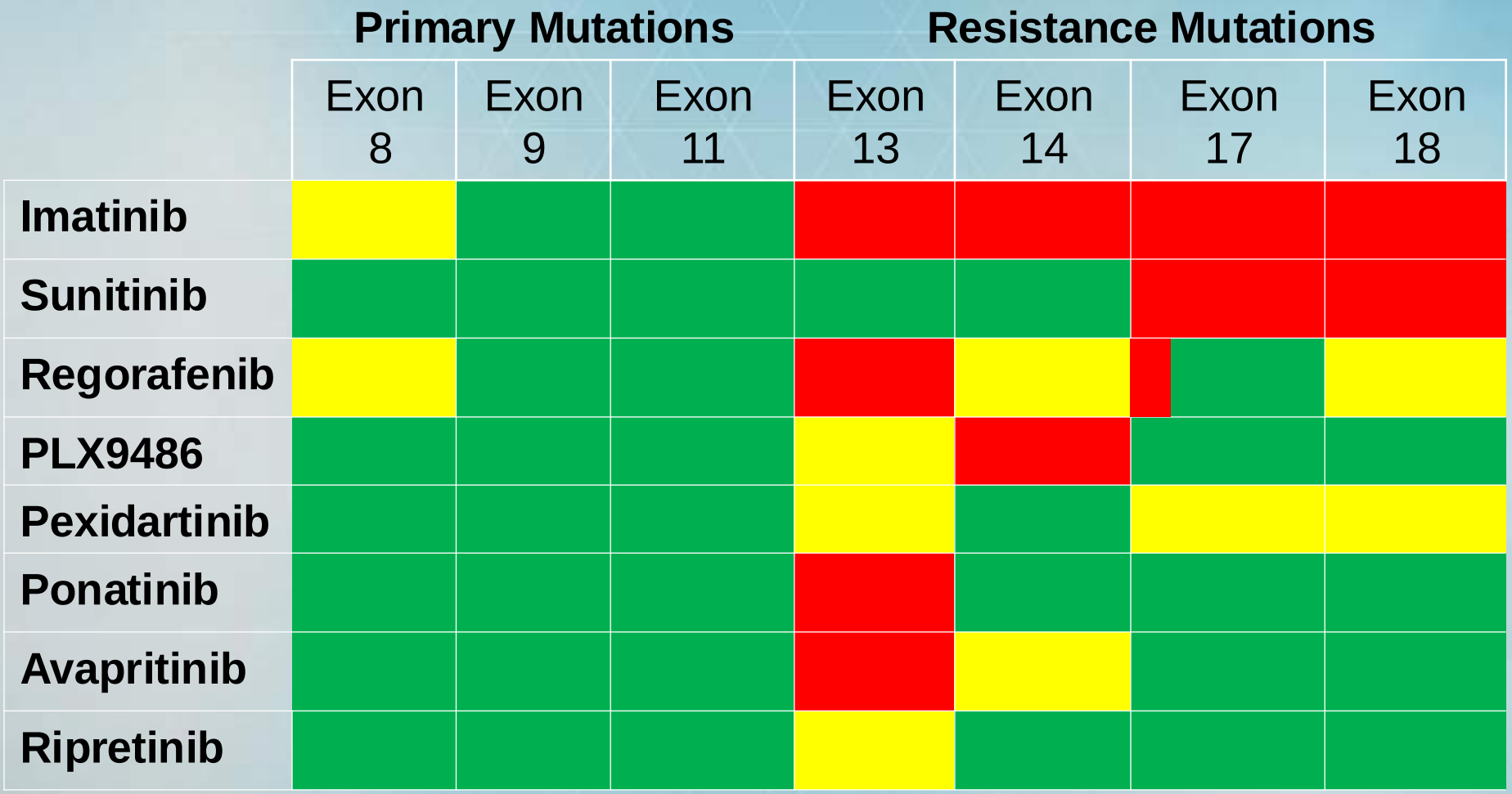
ATP/ADP Binding Site (V654)
EXON 13

Gate Keeper (T670)

Activation Loop (D820)
EXON 17

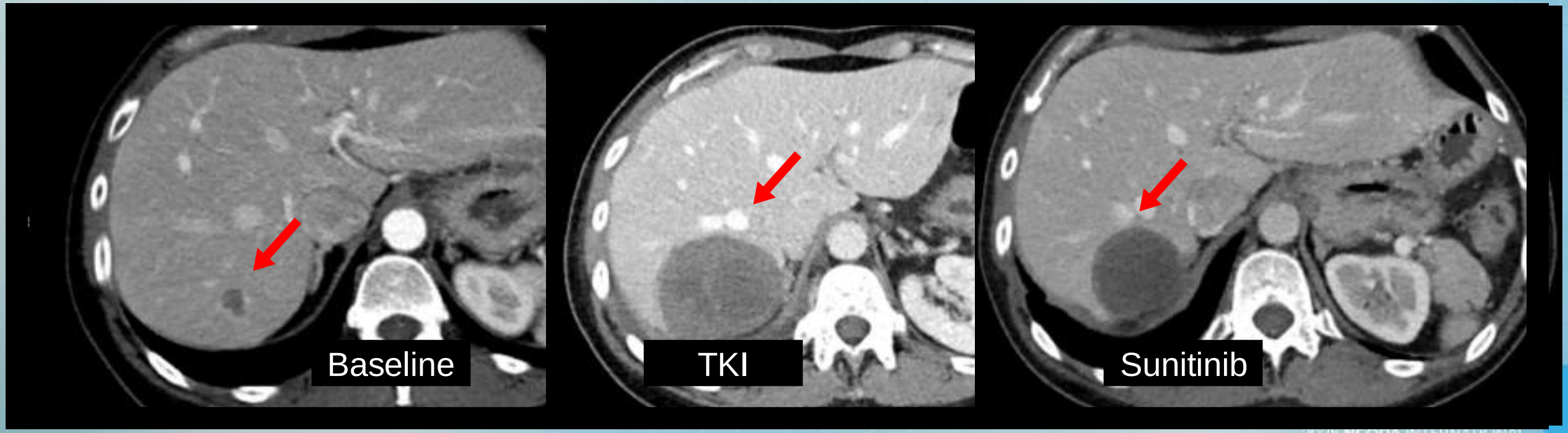
Chen, Trent, et al. Cancer Res 2004;64:5913-5919

Differential Sensitivity to TKI



Trent, CTOS 2017. Serrano C, *Br J Cancer* 2018. Gramza AW, *Clin Cancer Res* 2009. Heinrich MC, *ASCO*2013. Arshad J, *JCO Precis Oncol* 2020.

- 52 YO woman with small intestine, ***KIT* exon 11 (L576P)** mutant, GIST with liver metastases
- Initial response to imatinib durable for 2 years
- Progressive on imatinib placed on *KIT* inhibitor a**vapritinib**, rapid progression
- ctDNA revealed ***KIT* exon 13 V654A** resistance mutation
- Placed on s**unitinib** to target *KIT* exon 11 primary and *KIT* exon 13 resistance mutations



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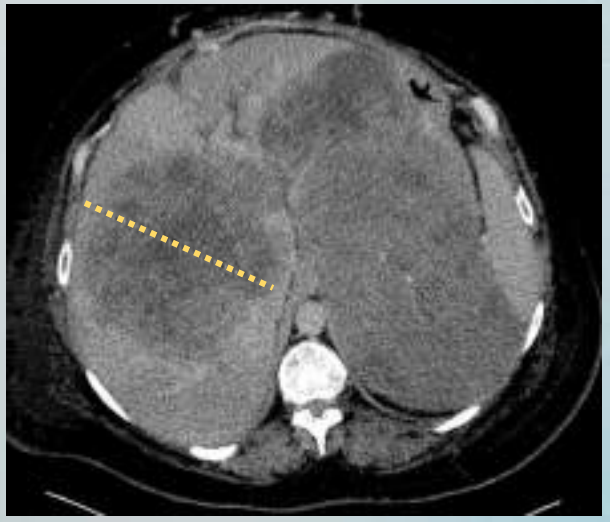
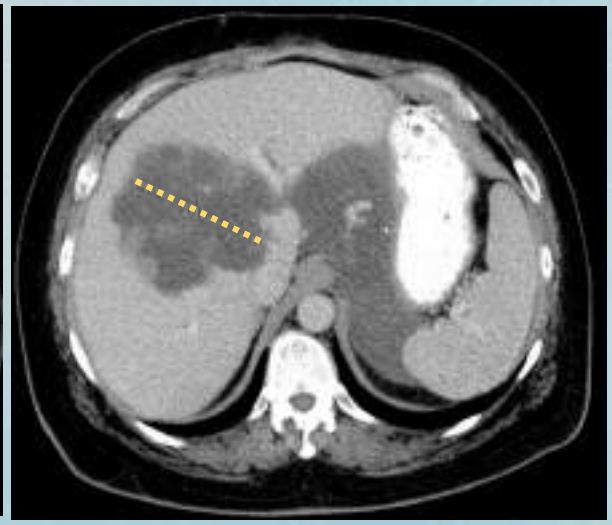
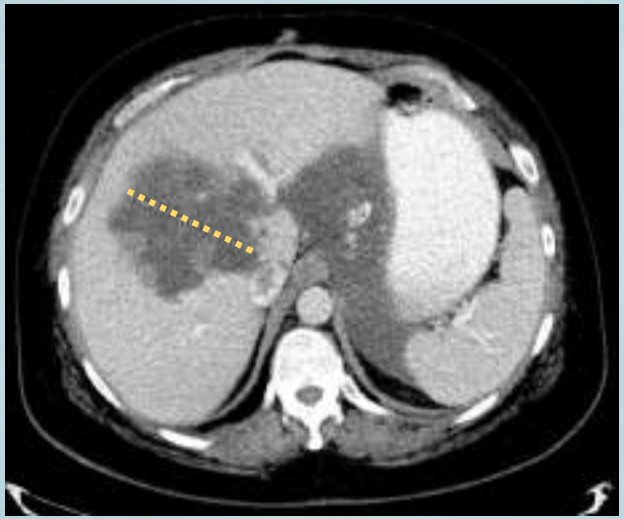
KIT exon 11 resistant GIST with Exon 17 resistance mutation



*Baseline; **before** ponatinib*



*After **6 months** of ponatinib*



*After **12 months** of ponatinib*

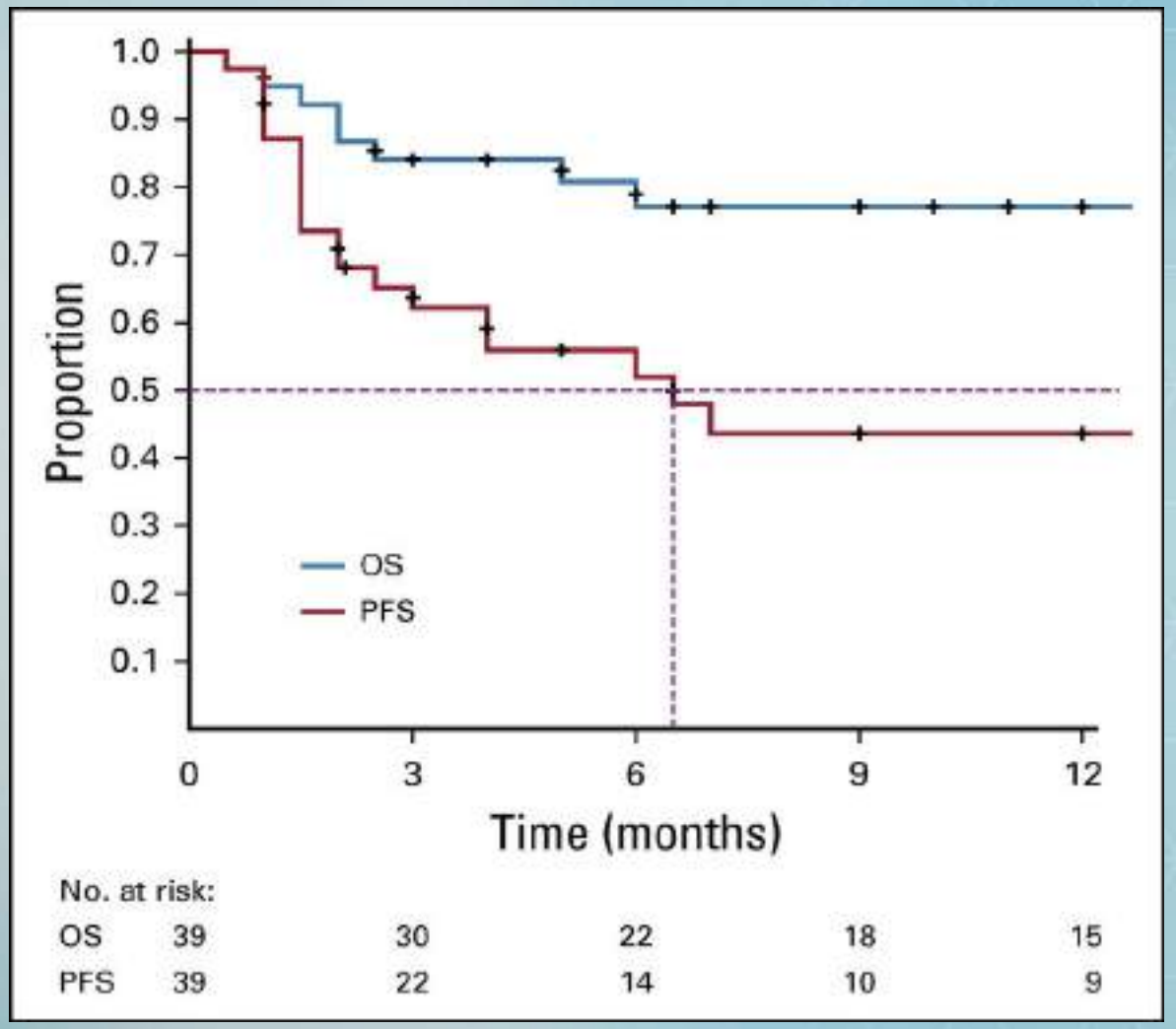
Utility of ctDNA in GIST

	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 and Progressive	21	21	100%

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

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

Outcome in the era of ctDNA IN GIST (N=39)

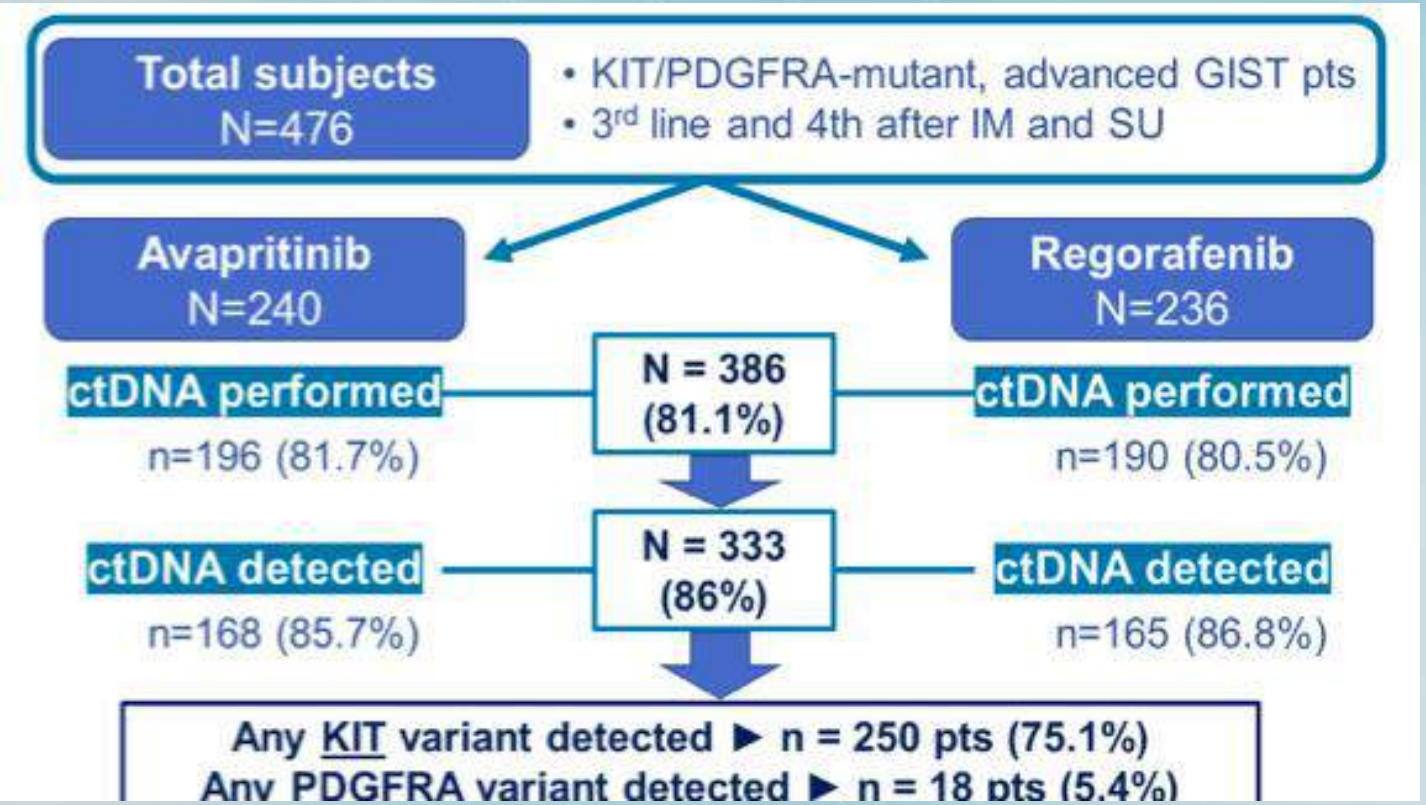


12 months from ctDNA testing (*n* = 39):

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

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

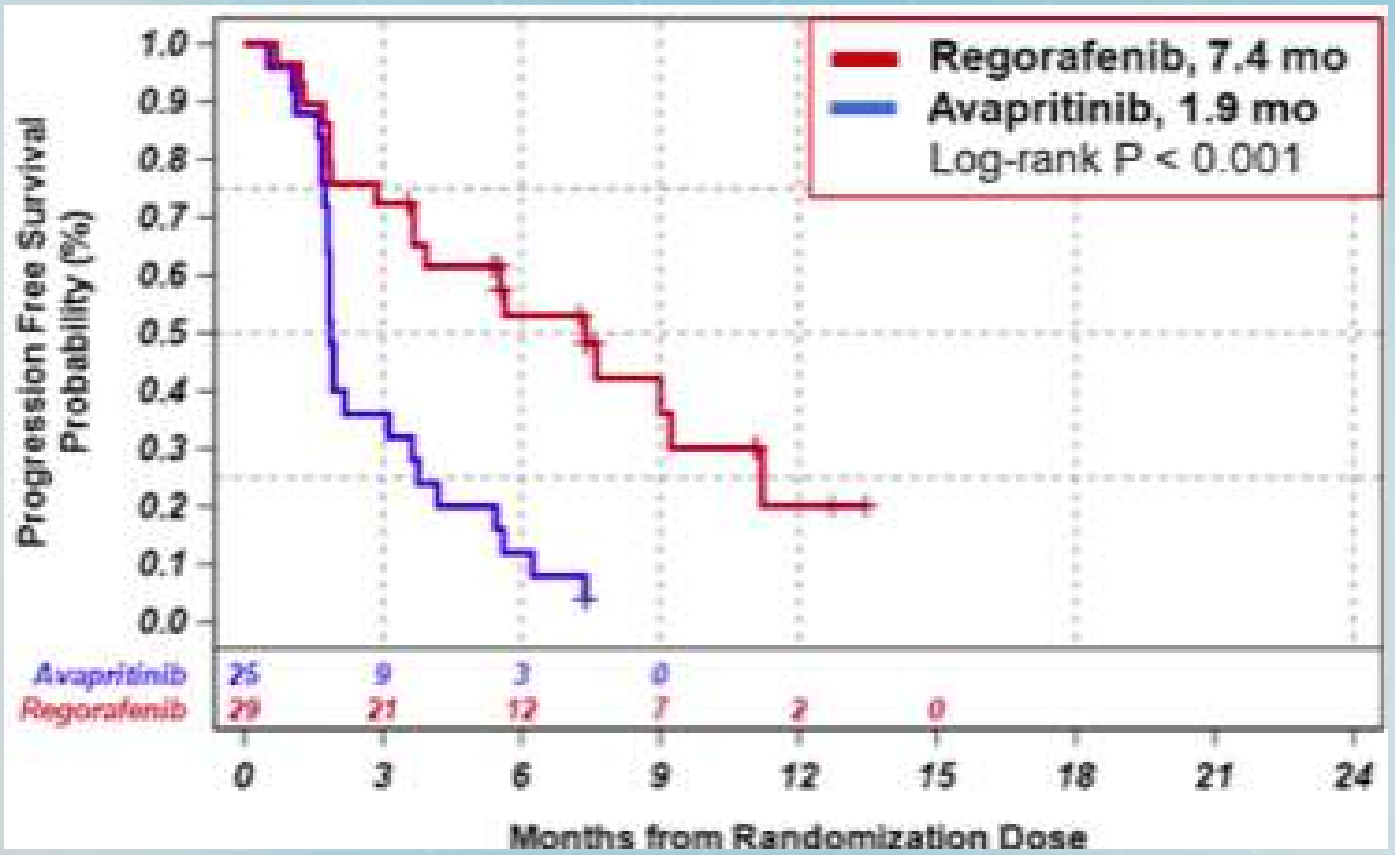
Voyager Trial ctDNA Analysis



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

Serrano, Trent, et al. ASCO 2022.

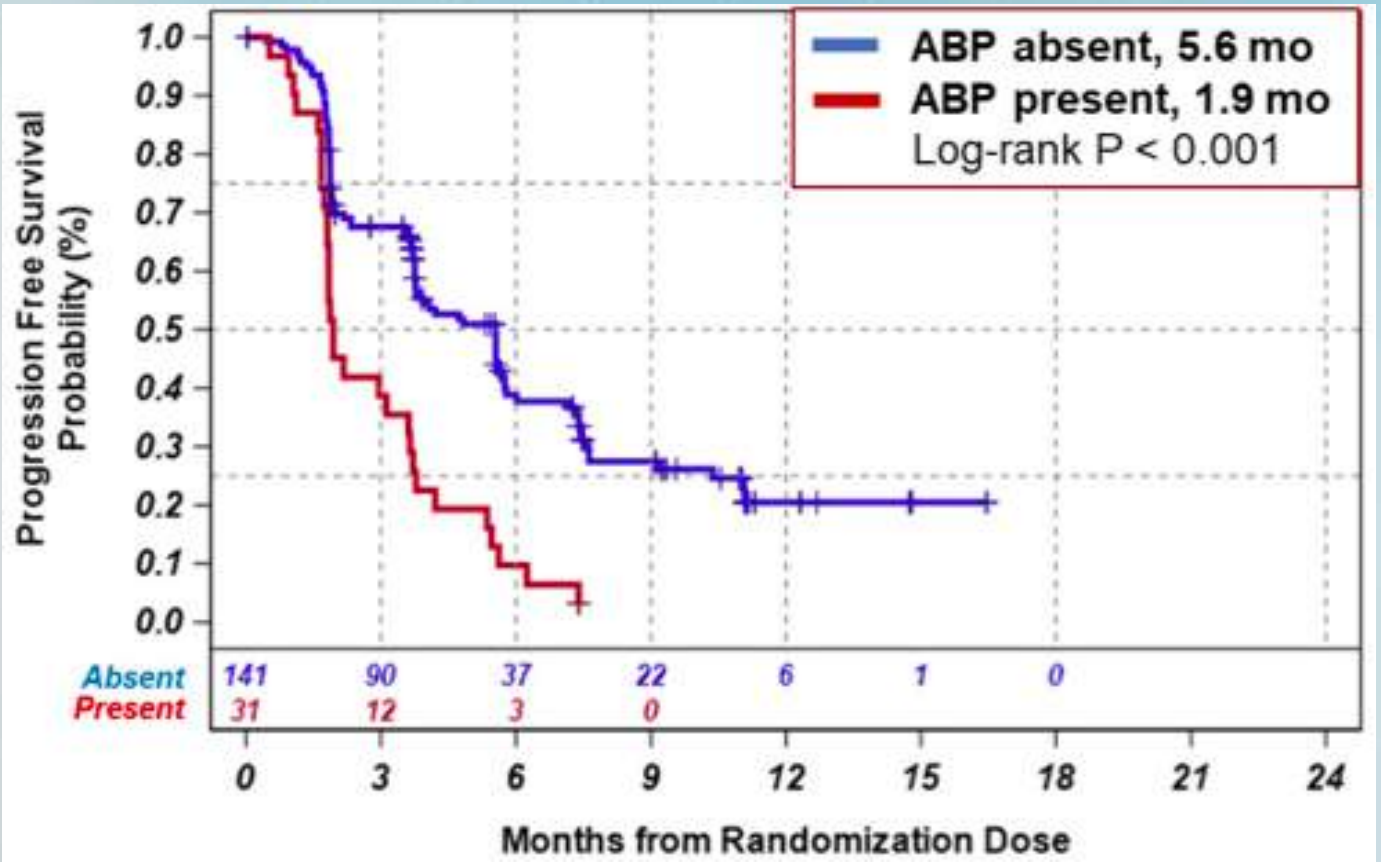
VOYAGER Trial



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

Serrano, Trent, et al. ASCO 2022.

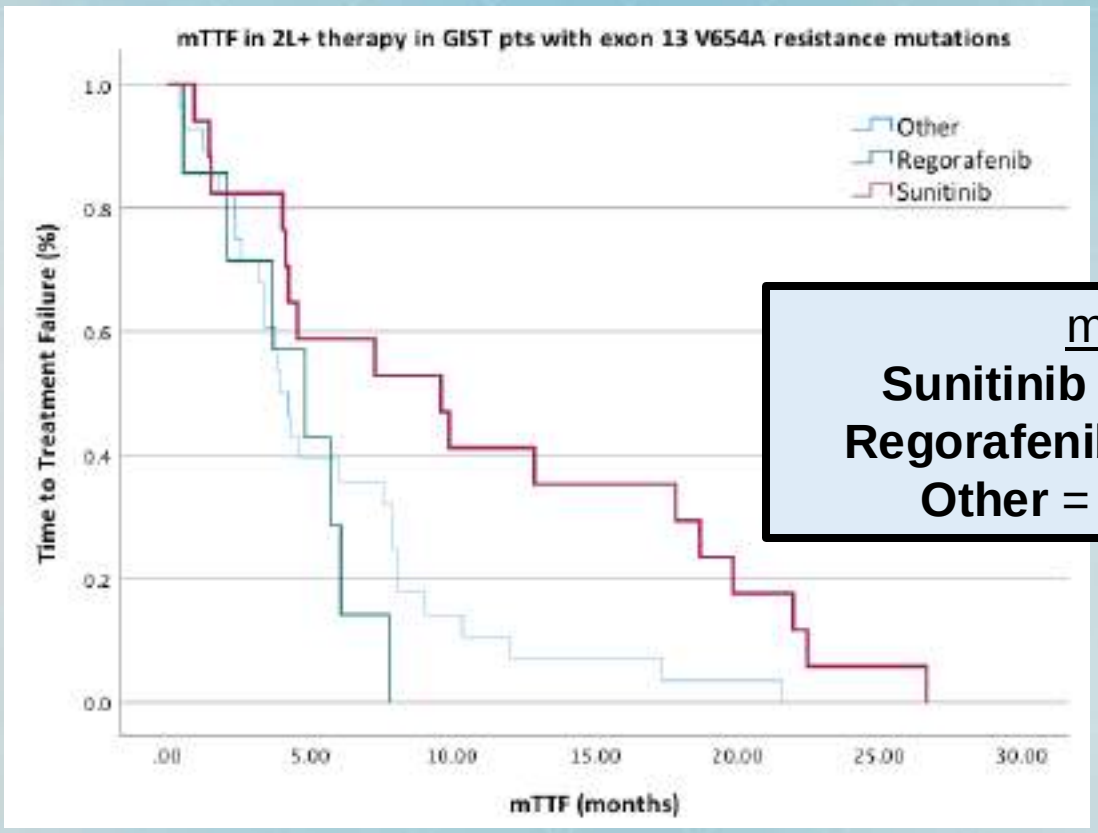
VOYAGER Trial



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

Serrano, Trent, et al. ASCO 2022.

2L+ mTTF KIT Exon13 (V654A) Patients



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

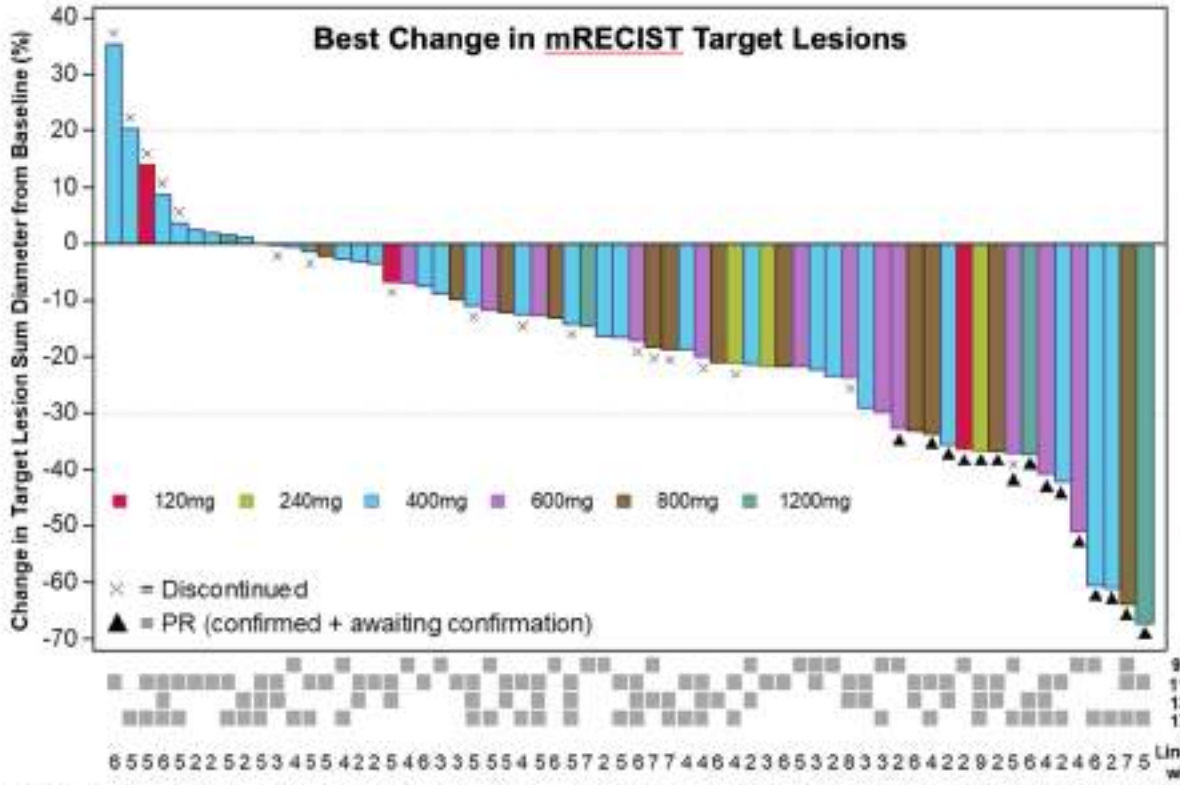
HR = 0.677
CI: 0.49-0.93
p=0.01

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

Bialick, Trent CTOS 2023

IDRX-42 Promising Activity

Promising anti-tumor activity in heavily pretreated GIST patients



mRECIST Response Evaluable for Efficacy†

	All Patients N=66	2nd Line Patients N=14
Partial Response, n (%) *confirmed + awaiting confirmation*	15 (23) ††	6 (43) ‡
Median time to response, months	2.6	3.7
Median follow-up, months	5.6	3.0

†Efficacy evaluable defined as all patients with at least 1 postbaseline disease assessment or clinical progression or death before first postbaseline disease assessment. Disease assessments performed at baseline, 4 weeks, 8 weeks and every 8 weeks thereafter; ††Includes 3 PRs awaiting confirmation; ‡Includes 2 PRs awaiting confirmation. Of 2nd line patients with opportunity for ≥16 weeks follow up, 6/7 achieved a PR; 400 mg and 800 mg capsule equivalent dose levels include patients treated with 300 mg QD tablets and 600 mg QD tablets, respectively; mRECIST, modified RECIST; PR, partial response; QD, once daily; Data cutoff date: 26 April 2024

2024 ASCO ANNUAL MEETING #ASCO24

PRESENTED BY: Dr. Patrick Schöffski

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Schöffski P, et al. StrateGIST 1: A first-in-human (FIH), phase 1 study of IDRX-42 in patients with advanced gastrointestinal stromal tumors (GIST). J Clin Oncol. 2024;42(16_suppl):11501. Presented at: 2024 ASCO Annual Meeting; May 31–June 4, 2024; Chicago, IL.

IDRX-42 Promising Activity

mRECIST Response Evaluable for Efficacy†	All Patients N=66	2nd Line Patients N=14
Partial Response, n (%) *confirmed + awaiting confirmation*	15 (23) ††	6 (43) ‡
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Schöffski P, et al. StrateGIST 1: A first-in-human (FIH), phase 1 study of IDRX-42 in patients with advanced gastrointestinal stromal tumors (GIST). J Clin Oncol. 2024;42(16_suppl):11501. Presented at: 2024 ASCO Annual Meeting; May 31–June 4, 2024; Chicago, IL.

GIST Subtypes and Treatment

- Kit exon 11: **Imatinib 400 mg**
- Kit exon 9: **Imatinib 800mg (or tolerated dose)**
- PDGFR D842V: **Avapritinib**
- SDH deficiency: **Temozolomide or FGFR inhibitor**
- Raf V600E: **Raf inhibitor**
- NF-1, Ras: **Raf or Mek inhibitor**
- PI3K: **mTOR inhibitor**
- TRK fusion – **NTRK inhibitor (Laro, Entrectinib)**
- KIT resistance mutations
  - Exon 13 (ATP binding site): **Sunitinib 37.5 mg daily**
  - Exon 17 (A-loop): **Regorafenib or Ripretinib**

Clinical Trials for GIST Patients

- Phase 1 Studies
  - o Ripretinib + DCC-3116 (Autophagy inhibitor)
  - o DCC-3009 (new KIT inhibitor)
  - o NN-3201 KIT Antibody Drug Conjugate
  - o Imatinib + Ziftomenib (Oral Menin Inhibitor)
  - o IDRX-42 (new KIT inhibitor)
  - o NB-003, THE-630
- Phase 2 ctDNA-guided therapy for GIST patients (IntellliGIST)
  - o Any line prior therapy
  - o Must have exon 13/14 or 17/18 resistance mutation
  - o ctDNA testing provided
- Phase 3
  - o Randomized Sunitinib +/- bezuclastinib (CGT-9486) in 2nd line for GIST patients
  - o Randomized Ripretinib vs Sunitinib in KIT exon 17/18 resistant GIST patients (Insight)

Source: ClinicalTrials.gov and ASCO/ESMO 2024–2025 trial updates.

Sylvester Comprehensive Cancer Center

GIST/Sarcoma Team

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- Emanuela Palmerini
- Emily Jonczak
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- Elizabeth Montgomery
- Nasir Ud Din
- Jay-Lou Torres

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- Francesco Alessandrino

Nurse Practitioner
- Morgan Smith
- Solange Sierra
- Ali Naveda
- Zulay Cha ng

Nursing
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- Rosario Jara
- Francess Donna

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- Emily MacFarlane

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- Mo Al Maaieh

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- Raphael Yechieli
- Aaron Wolfson

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- Frank Civantos

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- Mauricio Pipkin

Interventional Radiology
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- Felipe de Souza

Gynecologic Oncology
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- Matt Pearson
- Abed Sinno

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- Julie de Leon
- Leo Wright

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- Zhefeng Duan
- Luyuan Li
- Karina Galoian
- Josie Eid

Social Work
- Marlene Morales
- Adriana Alvarez (AYA)

THANK YOU!

QUESTION 2

After this session, how confident are you in recalling strategies to optimize treatment for GIST based on different mutational profiles?

a. Very confident – I can readily apply this in patient care
b. Moderately confident – I understand but would need additional resources
c. Not confident – I still need more education on this topic

Get the GIST of Precision Medicine

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