



LIFEFEST2026

Nashville



**Latest From the GIST Stage:
Treatment for after Standard Therapy**

Dr. Jonathan Trent

Treatment For After Standard Therapy

ctDNA and Novel TKI

LifeFest 2026

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GIST Medical Therapy

- Metastatic disease treated with tyrosine kinase inhibitors (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)

GIST Subtypes

Kit exon 11

Kit exon 9

KIT resistance mutations

Exon 13 (ATP binding site)

Exon 17 (A-loop)

PDGFR D842V

SDH deficiency

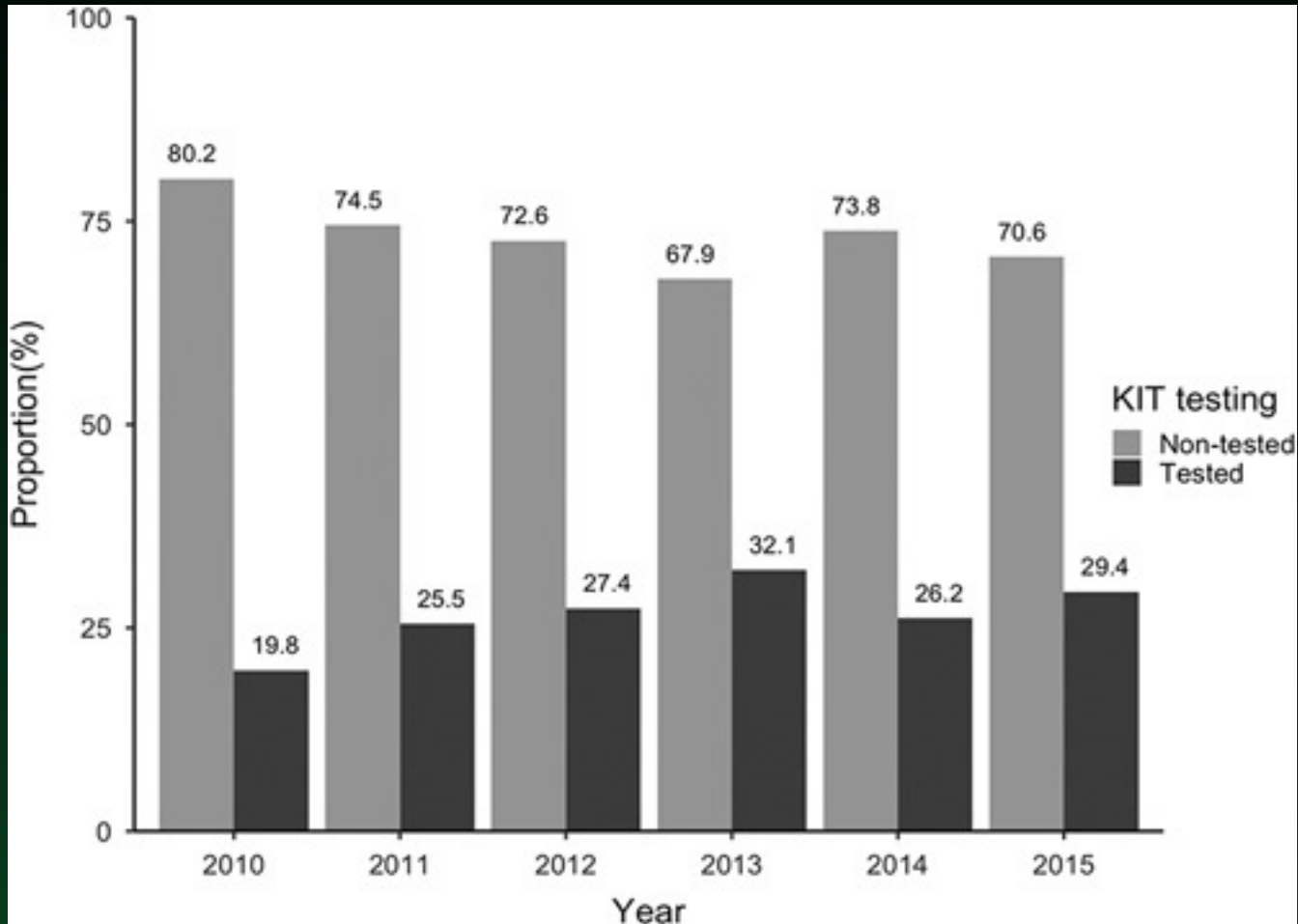
Raf V600E

NF-1, Ras

FGFR fusion

TRK fusion

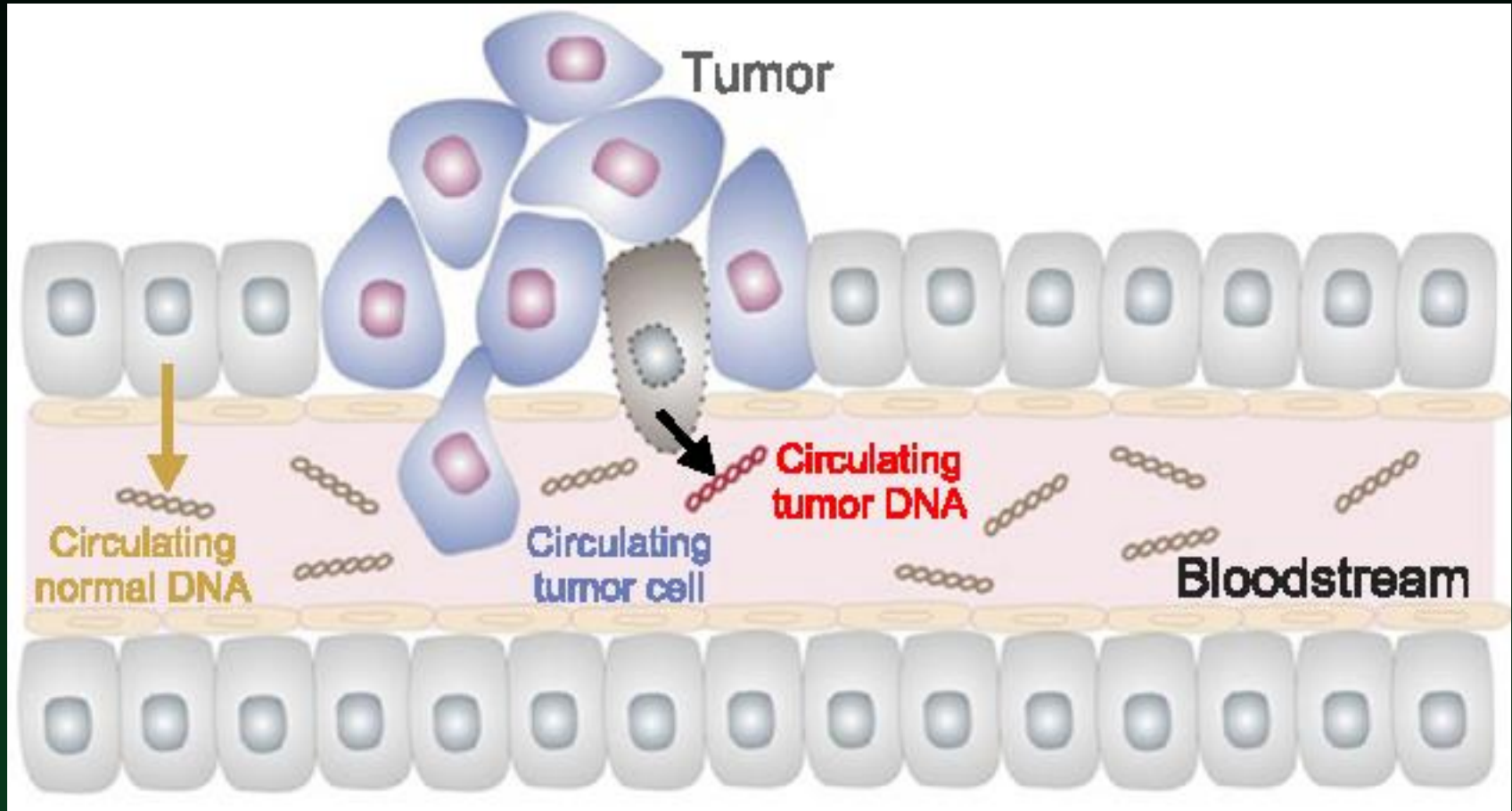
GIST mutation testing in US



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

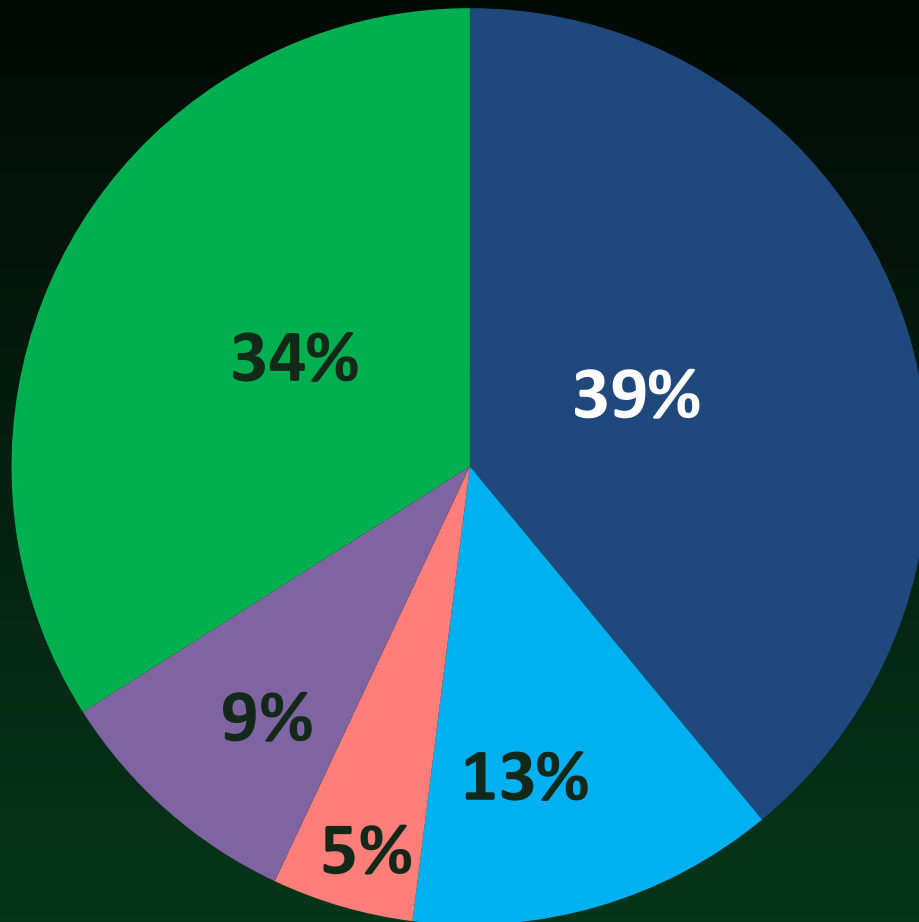
Mutation Testing From Blood (Liquid Biopsy)



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% ←

Distribution of Primary Mutations (%)



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

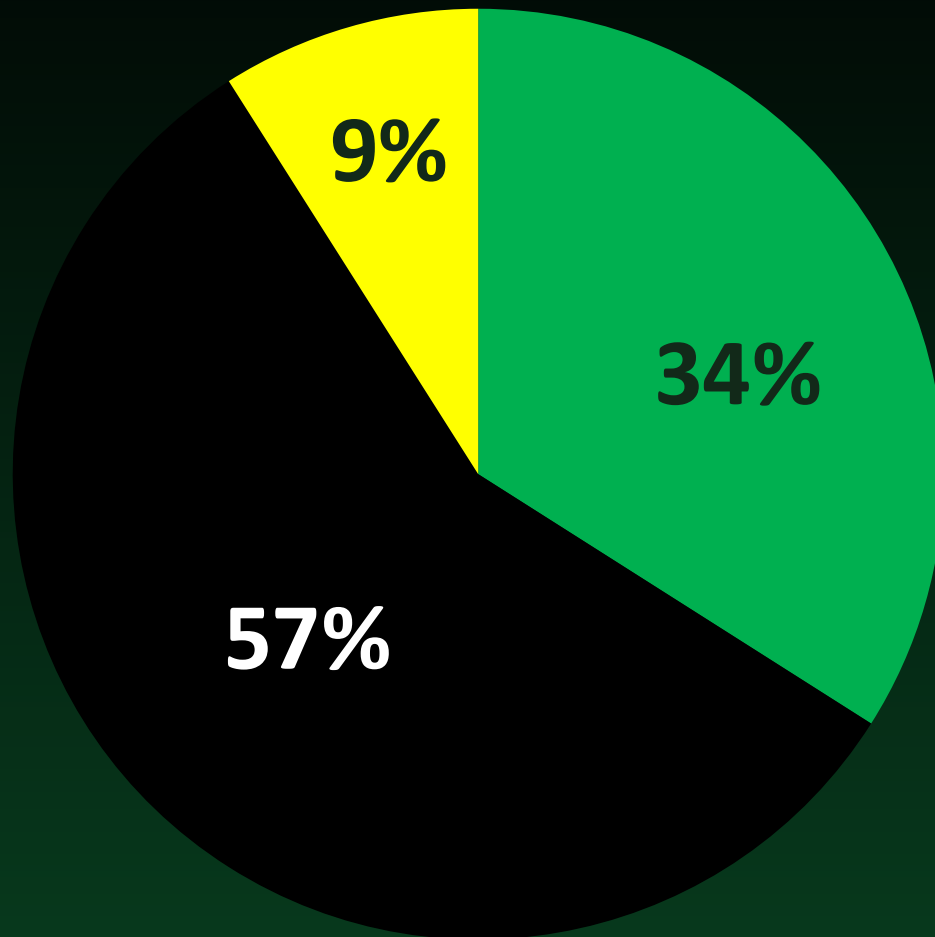
■ Kit exon 11

■ KIT exon 9

■ KIT other

Sunitinib Rechallenge

Resistance Mutations (%)



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

■ KIT Exon 13

■ KIT Exon 17

■ Other

Differential Sensitivity to TKI

	Primary Mutations				Resistance Mutations		
	Exon 8	Exon 9	Exon 11	Exon 13	Exon 14	Exon 17	Exon 18
Imatinib	Yellow	Green	Green	Red	Red	Red	Red
Sunitinib	Green	Green	Green	Green	Green	Red	Red
Regorafenib	Yellow	Green	Green	Red	Yellow	Green	Yellow
PLX9486	Green	Green	Green	Yellow	Red	Green	Green
Pexidartinib	Green	Green	Green	Yellow	Green	Yellow	Yellow
Ponatinib	Green	Green	Green	Red	Green	Green	Green
Avapritinib	Green	Green	Green	Red	Yellow	Green	Green
Ripretinib	Green	Green	Green	Yellow	Green	Green	Green

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

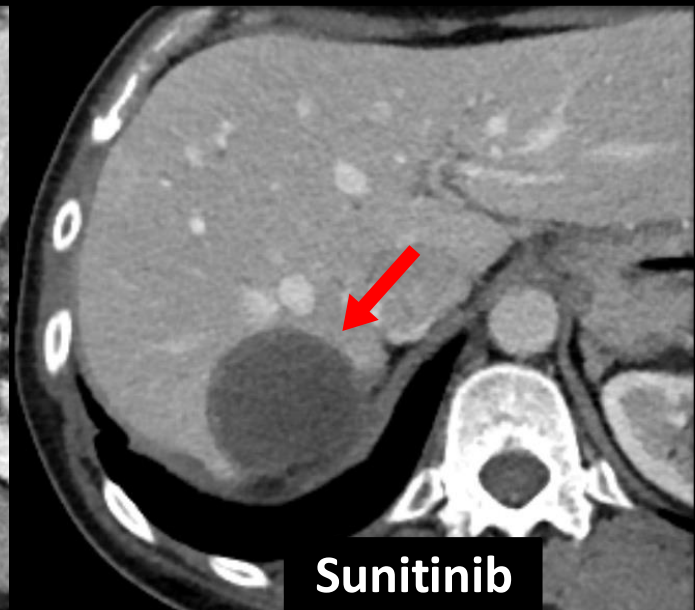
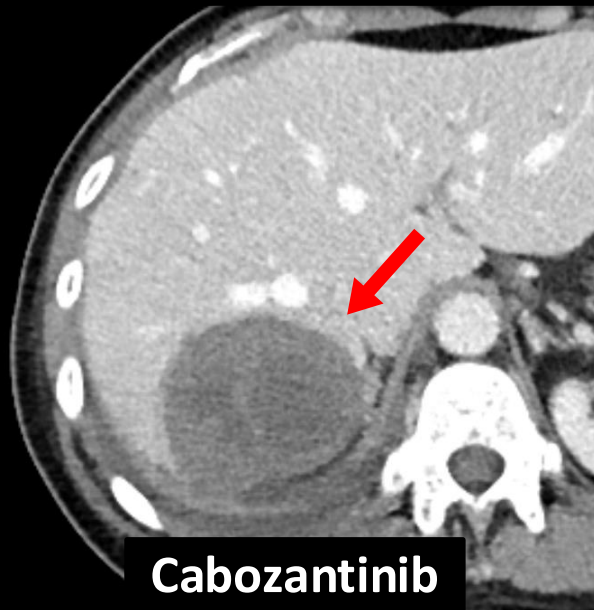
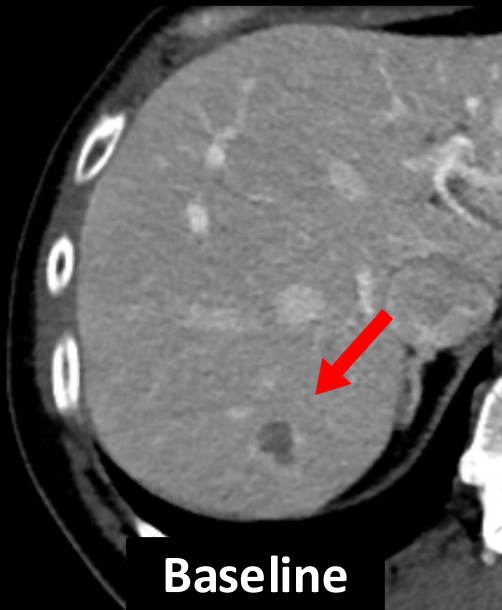
Trent, CTOS 2017

Serrano BJC 2018

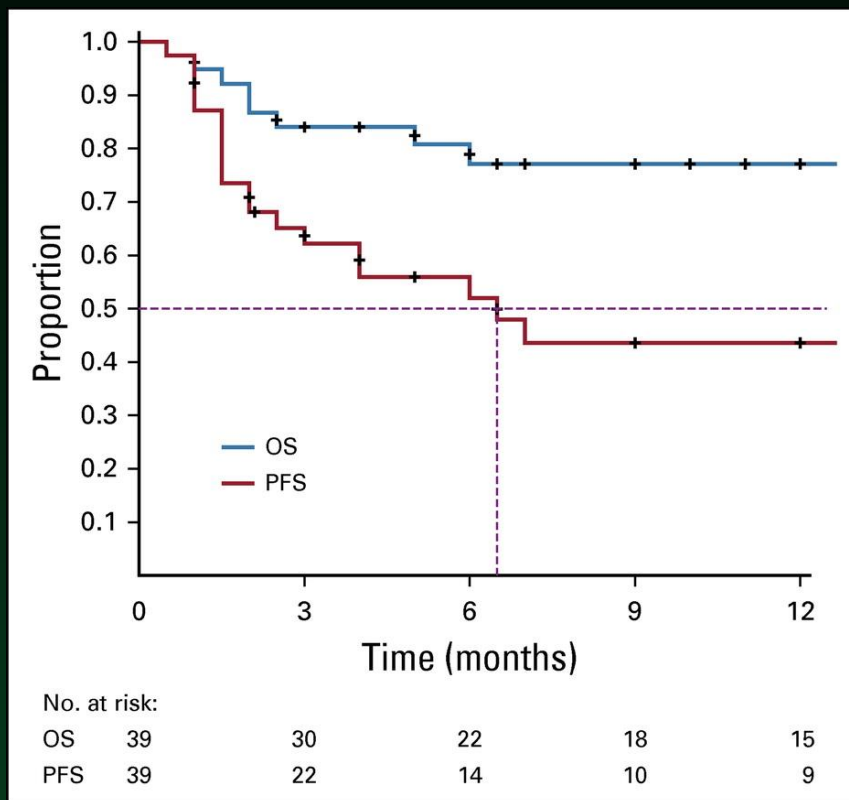
Gramza et al, Clinical Cancer Research 15:7510, 2009

Heinrich et al, ASCO 2013 Poster/Abstract 10509

- 52 YO woman, small intestine GIST, **KIT exon 11 (L576P)**, liver metastases
- Initial response to **imatinib** durable for 2 years then PD
- Treated with **sunitinib**, **regorafenib**, **ripretinib**, **cabozantinib** over 3 years all PD
- ctDNA revealed KIT exon 13 V654A resistance mutation
- Placed on **sunitinib** to target KIT exon 11 primary and KIT exon 13 resistance mutations



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

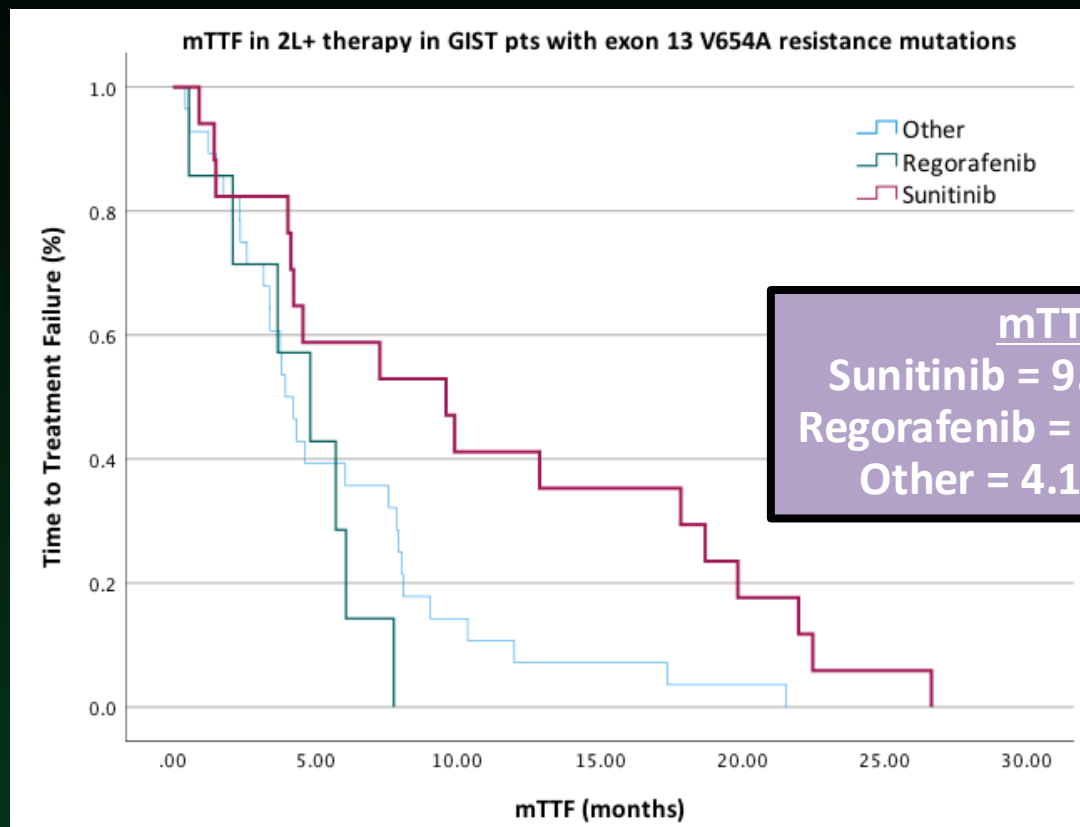


12 months from ctDNA testing ($n = 39$):

OS = 79.5%; CI 0.66-0.92

PFS = 46.2%; CI 0.32-0.65

2L+ mTTF *KIT* EXON 13 (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

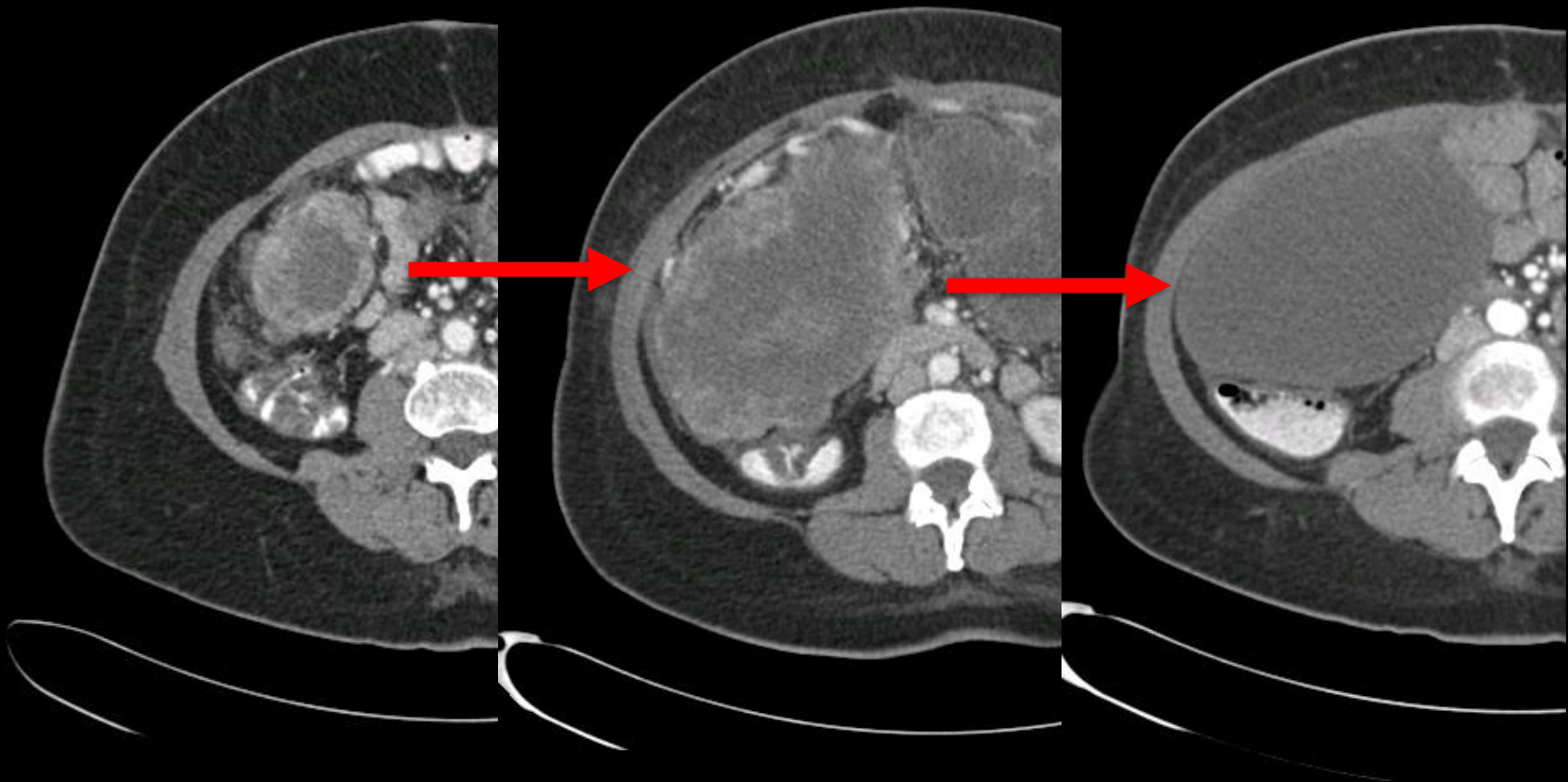
Imatinib Dose Escalation

GIST Patient Initial Therapy

KIT Exon 9 Mutation

Imatinib 400 mg

Imatinib 800 mg



Clinical Trials

Remember...

- A clinical trial is a **scientific method**
- A clinical trial should be **ethically** and scientifically sound
- A clinical trial should be ethically and scientifically sound, **while providing a therapeutic option for patients**

Objectives

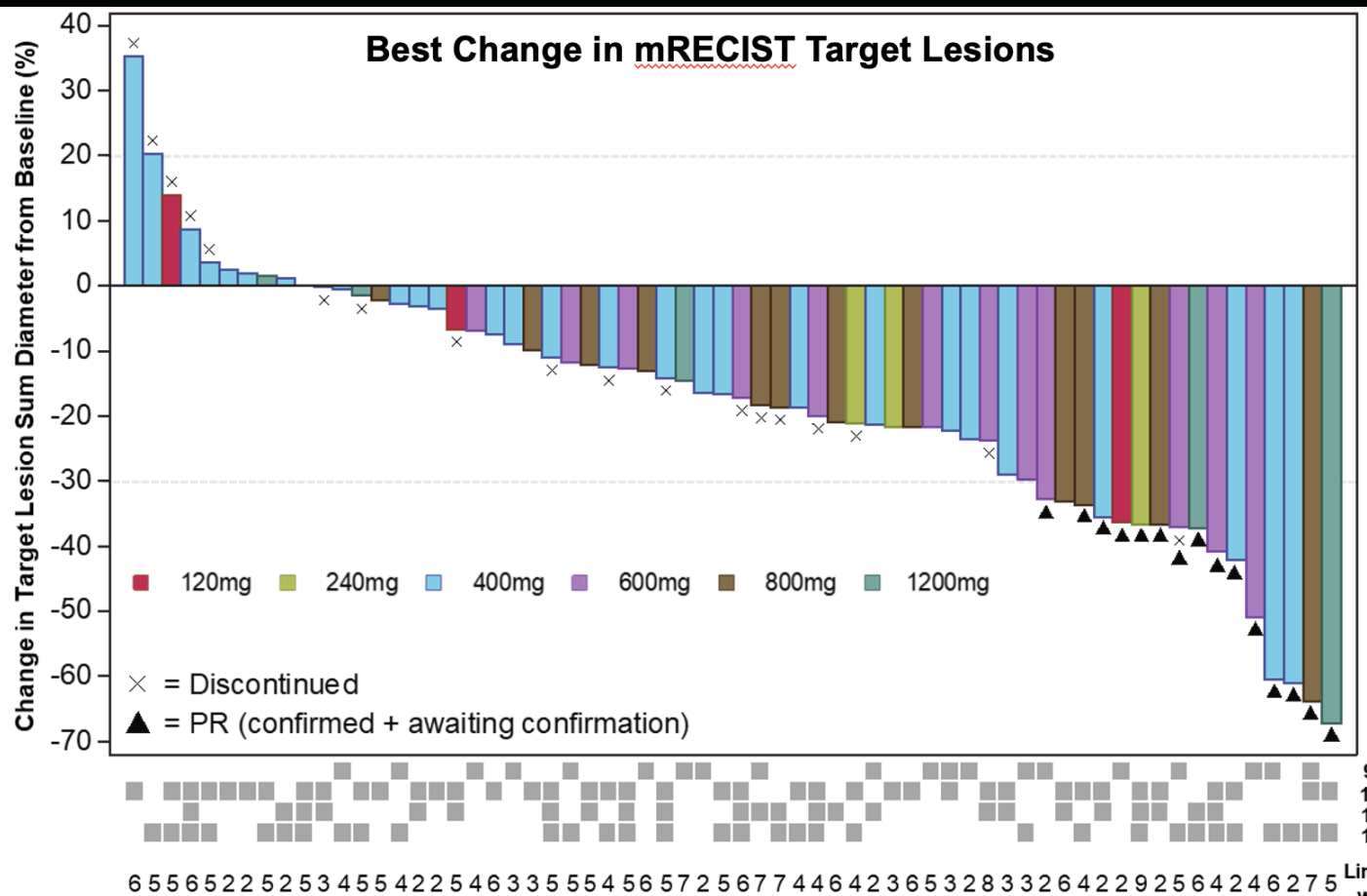
- **Phase I (first in human)**
 - To determine recommended Phase II dose
 - To assess efficacy to understand whether expansion is warranted
 - To assess safety
- **Phase I dose expansion or Phase II**
 - To assess safety at a single dose in more patients
 - To assess efficacy
- **Phase III**
 - To assess small differences in efficacy between therapies (drug, dose, formulation, BSC)

IDRX-42 Promising Activity

Next Generation KIT Inhibitor

<u>mRECIST Response</u> Evaluable for Efficacy [†]		
	All Patients N=66	2 nd Line Patients N=14
Partial Response, n (%)		
<i>confirmed + awaiting confirmation</i>	15 (23) ^{††}	6 (43) [‡]
Median time to response, months	2.6	3.7
Median follow-up, months	5.6	3.0

IDRX-42 Promising Activity



*Efficacy evaluable defined as all patients with at least 1 postbaseline disease assessment or clinical progression or death before first postbaseline disease assessment. Discontinued 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; 4/5 for 300 mg QD tablets and 600 mg QD tablets, respectively; mRECIST, modified RECIST; PR, partial response; QD, once daily; Data cutoff date: 28 April 2024

2024 ASCO
ANNUAL MEETING

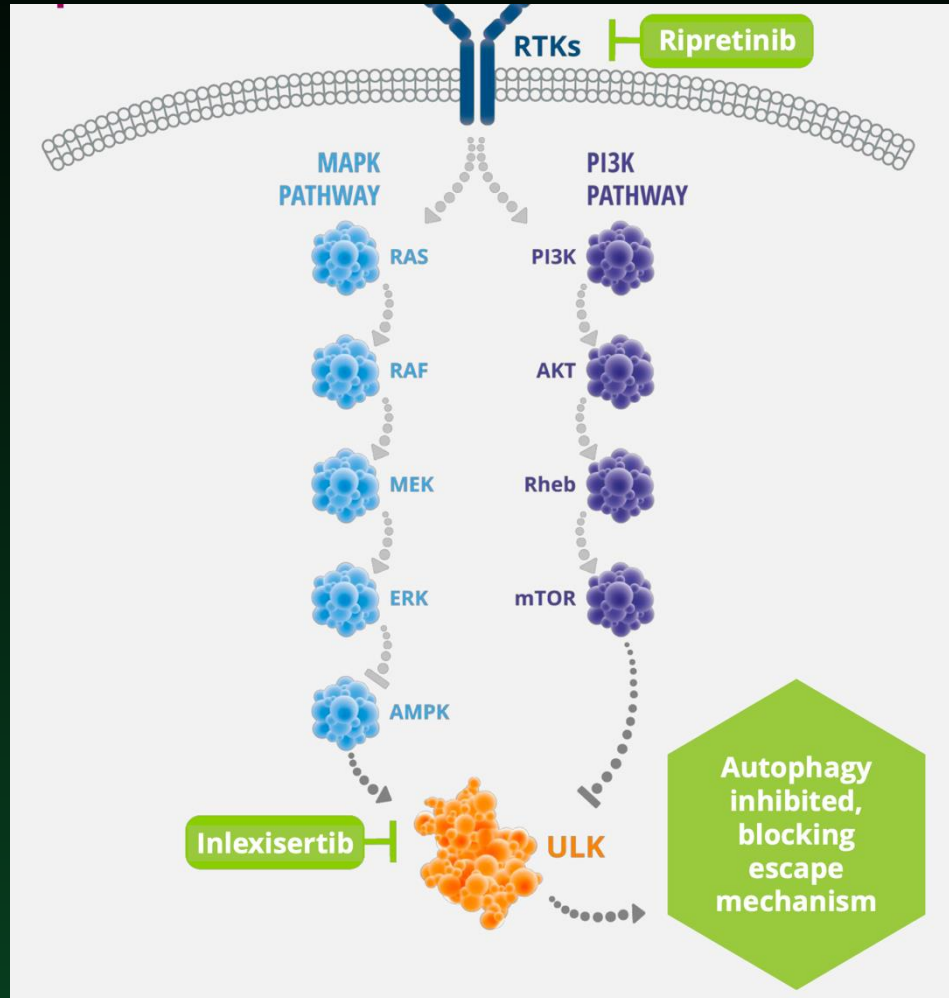
#ASCO24

PRESENTED BY: Dr. Patrick Schöffski

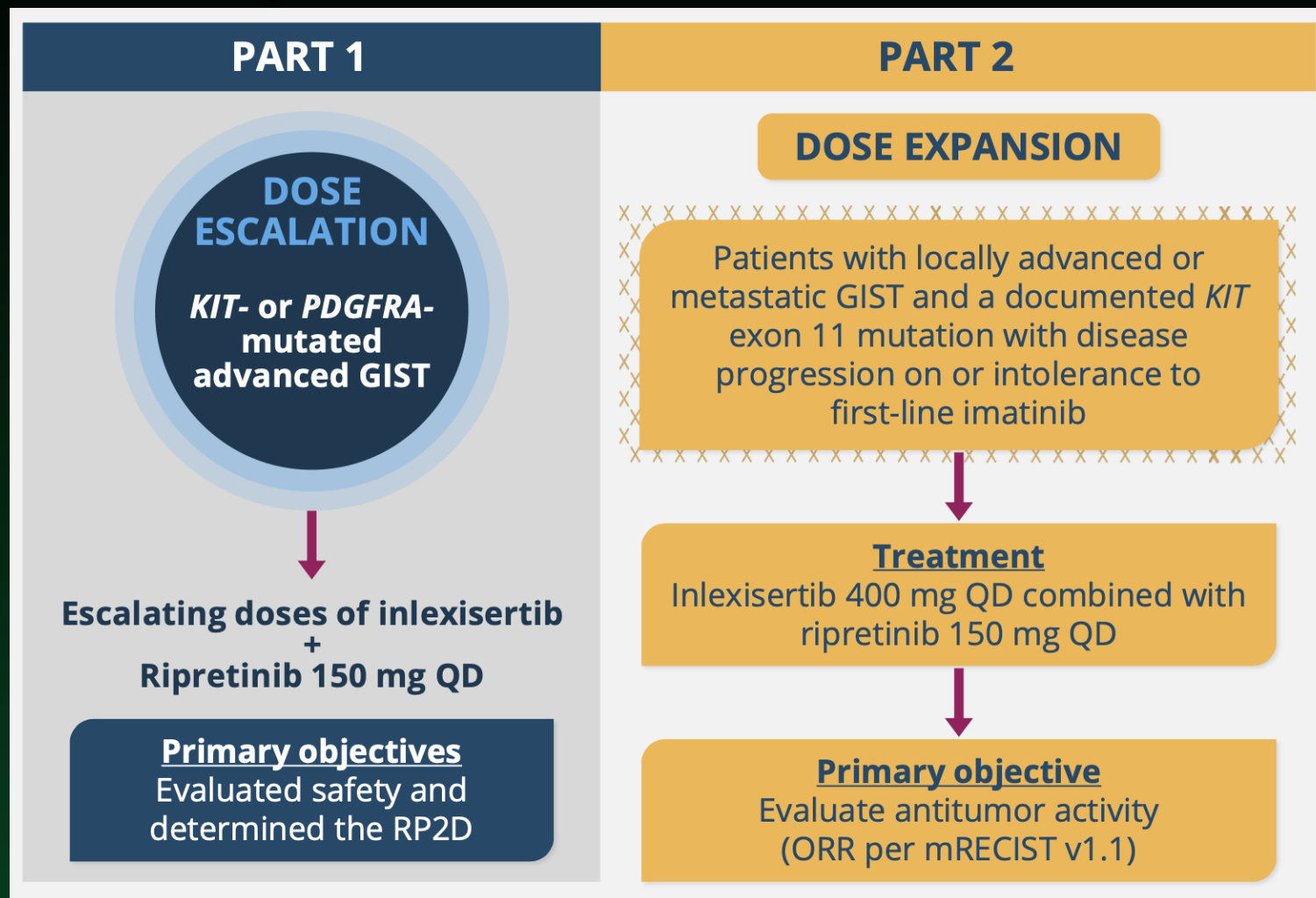
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Ripretinib + DCC-3116

Inlxisertib inhibits autophagy driven by ULK1/2 in response to RTK inhibition by ripretinib

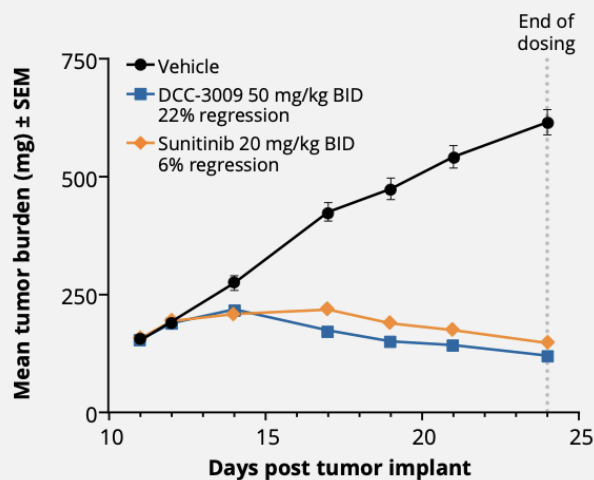


Ripretinib + DCC-3116

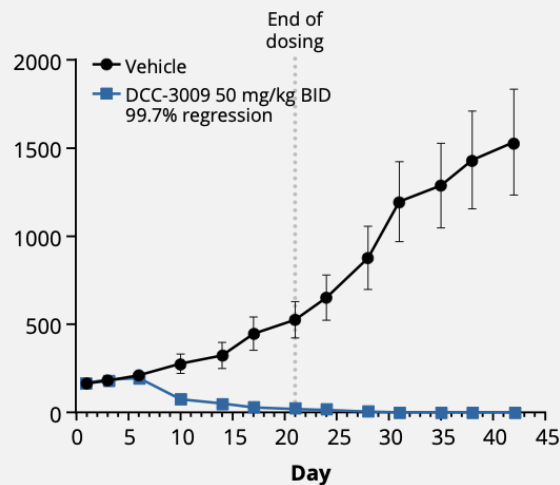


Robust antitumor activity of DCC-3009 in preclinical models

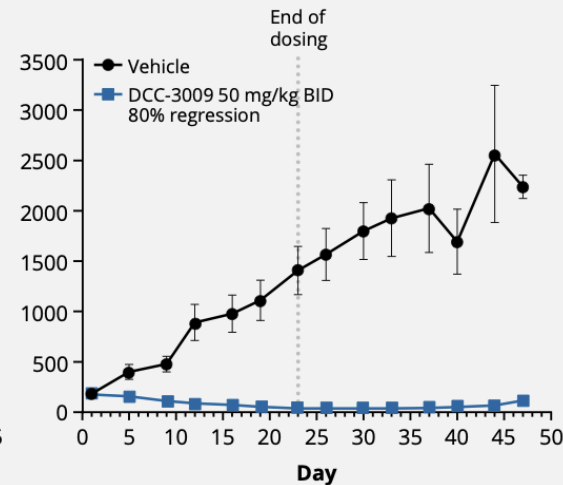
BaF3 *KIT* *AYdup/V654A* (exon 9/13)



GIST PDX *KIT* *delWK/Y823D* (exon 11/17)

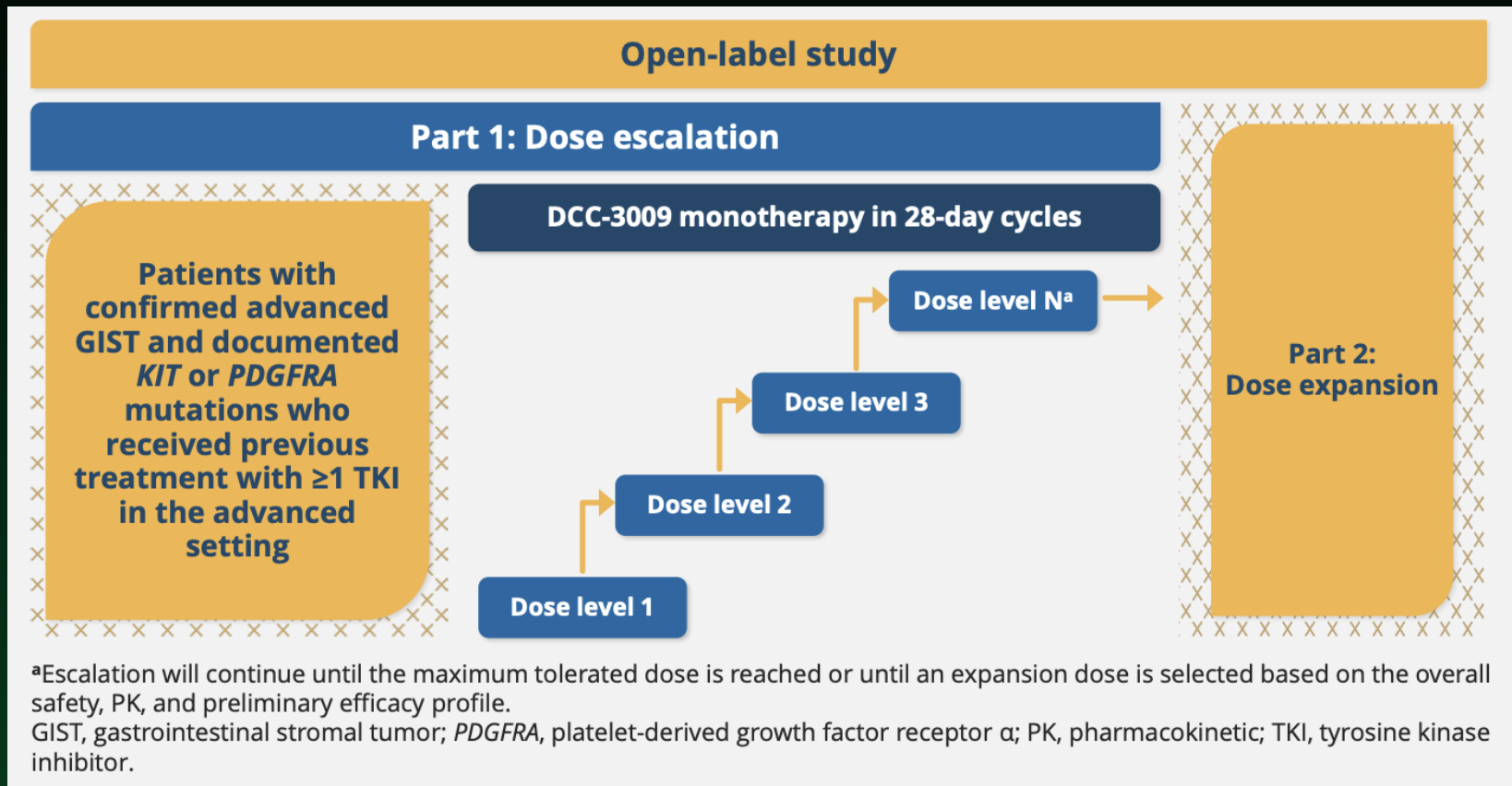


GIST PDX *KIT* *delWK/V654A* (exon 11/13)



When dosed orally BID, treatment with DCC-3009 led to tumor regression in *KIT* exon 9/13-, 11/13-, and 11/17-mutant models. BID, twice daily; GIST, gastrointestinal stromal tumor; PDX, patient-derived xenograft; SEM, standard error of the mean.

Dose escalation study design



Clinical Trials for GIST Patients

- Phase 1 Studies
 - Ripretinib + DCC-3116 (Autophagy inhibitor)
 - DCC-3009 (new KIT inhibitor)
 - NN-3201 KIT Antibody Drug Conjugate
 - Imatinib + Ziftomenib (Oral Menin Inhibitor)
 - PRMT5i (MTAP deletion)
 - IDRX-42 (new KIT inhibitor)
 - NB-003
- Phase 2 ctDNA-guided therapy for GIST patients (IntelliGIST)
 - any line prior therapy
 - must have exon 13/14 or 17/18 resistance mutation
 - ctDNA testing provided
- Phase 3
 - IDRX-42 vs Imatinib first line
 - Imatinib + Kumquat vs Imatinib

Conclusions

- Mutation testing is **necessary** for optimal treatment outcome
- ctDNA testing at each instance of **progression**
- **Always** ask about clinical trials
- We are excited about new medicines **but don't forget**
 - Hepatic Arterial Embolization
 - Metastatectomy
 - Radiation Therapy
 - Imatinib dose escalation
 - Sunitinib Rechallenge

Sylvester Comprehensive Cancer Center

GIST Sarcoma Team

- **Medical Oncology**

- Jon Trent
- Gina D'Amato
- Emanuela Palmerini
- Emily Jonczak
- Steve Bialick
- Priscilla Barreto-Coelho
- Amrit Paudel
- Aditi Dhir

- **Pathology**

- Andrew Rosenberg
- Elizabeth Montgomery
- Nasir Ud Din
- Diego Montoya

- **Radiology**

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- Francesco Alessandrino
- Felipe de Souza
- Fabio Cardoso

- **Nurse Practitioner**

- Morgan Smith
- Solange Sierra
- Ali Naveda
- Zulay Chang

- **Orthopedic Oncology**

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- Tom Temple
- Brooke Crawford
- Erik Geiger
- Haley Prough

- **Surgical Oncology**

- Julie Grossman
- Nipun Merchant
- Alan Livingstone
- Dido Franceschi

- **Radiation Therapy**

- Crystal Seldon
- Raphael Yechieli
- Aaron Wolfson

- **Head & Neck Surgery**

- Don Weed
- Frank Civantos

- **Thoracic Surgery**

- Dao Nguyen
- Mauricio Pipkin
- Diego Avella

- **Interventional Radiology**

- Alan Sag
- Felipe de Souza

- **Gynecologic Oncology**

- Matt Schlumbrecht
- Matt Pearson
- Abed Sinno

- **Clinical Research**

- Irene Marino
- Julie de Leon
- Kirenia Correa

- **Lab Research**

- David Lombard
- Zhefeng Duan
- Robert Walker
- Karina Galoian
- Josie Eid

THANK YOU!

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