Emerging Strategies for the Treatment of Gastrointestinal Stromal Tumor (GIST)

FLASCO Rare Cancers 2026

Jon Trent, MD, PhD

Professor of Medicine
Director, Bone and Soft-tissue Sarcoma
Associate Director, Clinical Research
The University of Miami,
Sylvester Comprehensive Cancer Center

jtrent@med.miami.edu

@JTrentMDPhD

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

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

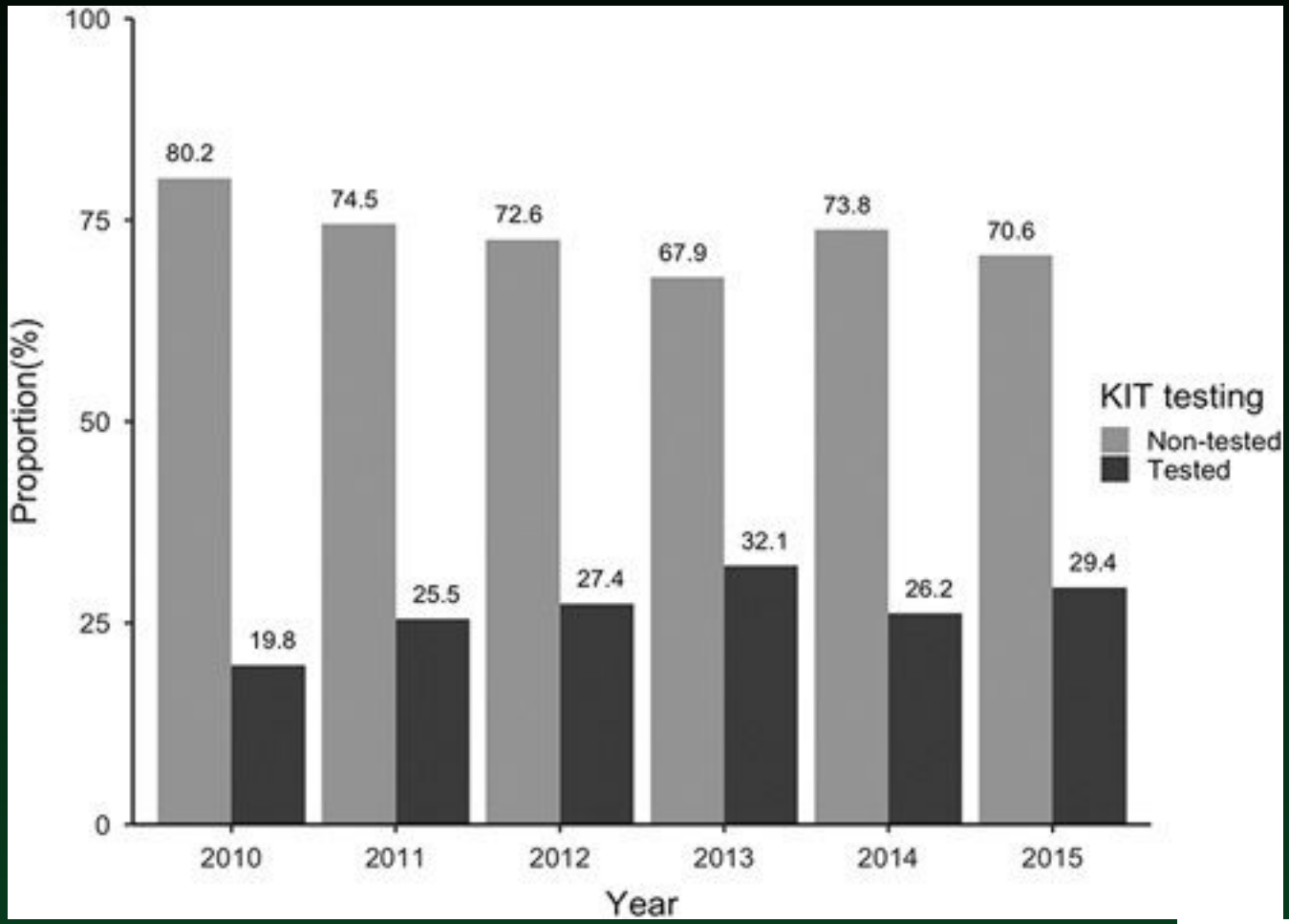
Raf V600E

NF-1, Ras

FGFR fusion

TRK fusion

GIST mutation testing in US

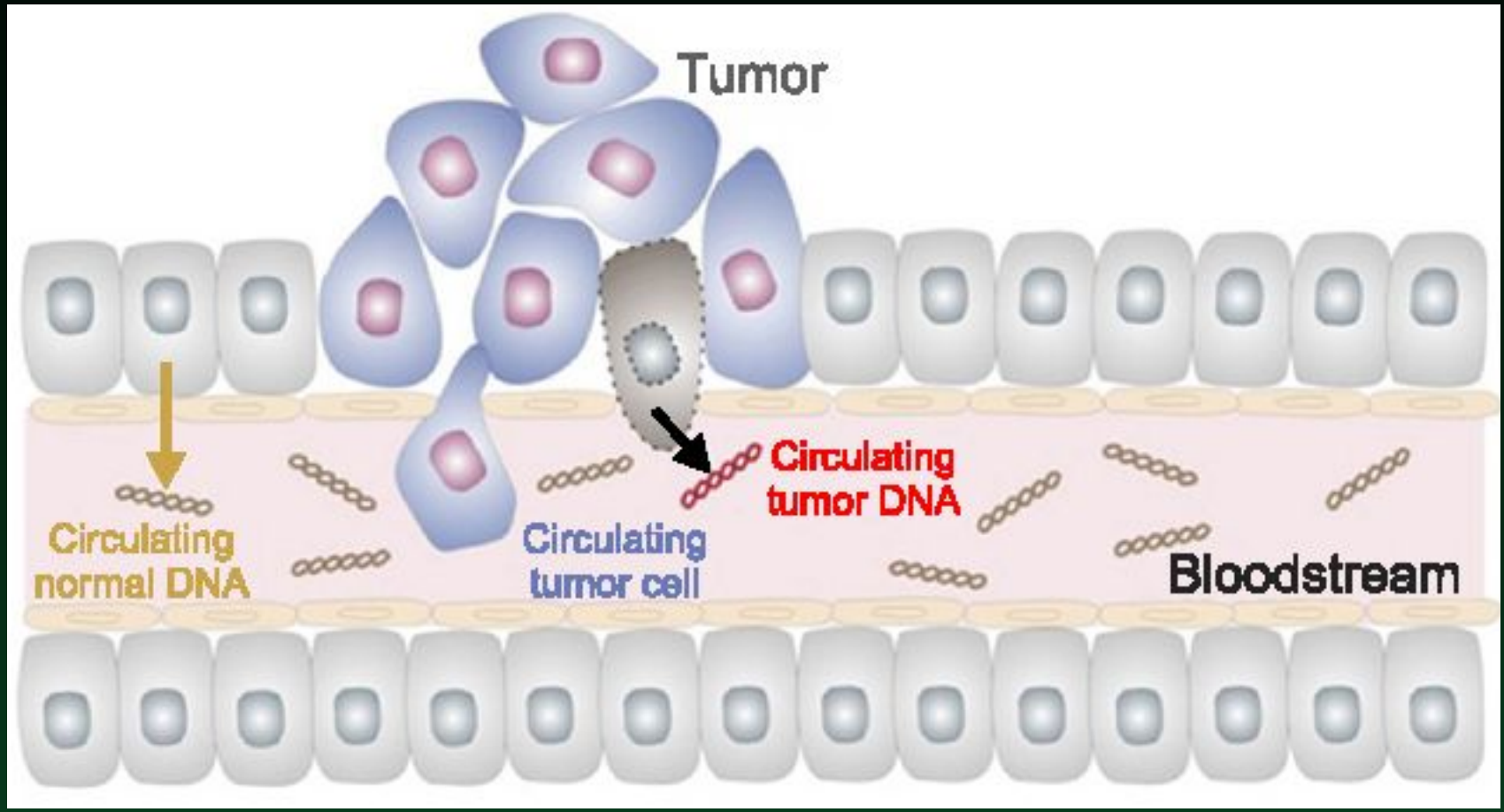


Florindez and Trent. American Journal of Clinical Oncology, April 2020. 43 (4), 270-278. Low Frequency of Mutation Testing in the United States: An Analysis of 3866 GIST Patients

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Circulating Tumor DNA

Mutation Testing From Blood (Liquid Biopsy)



SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

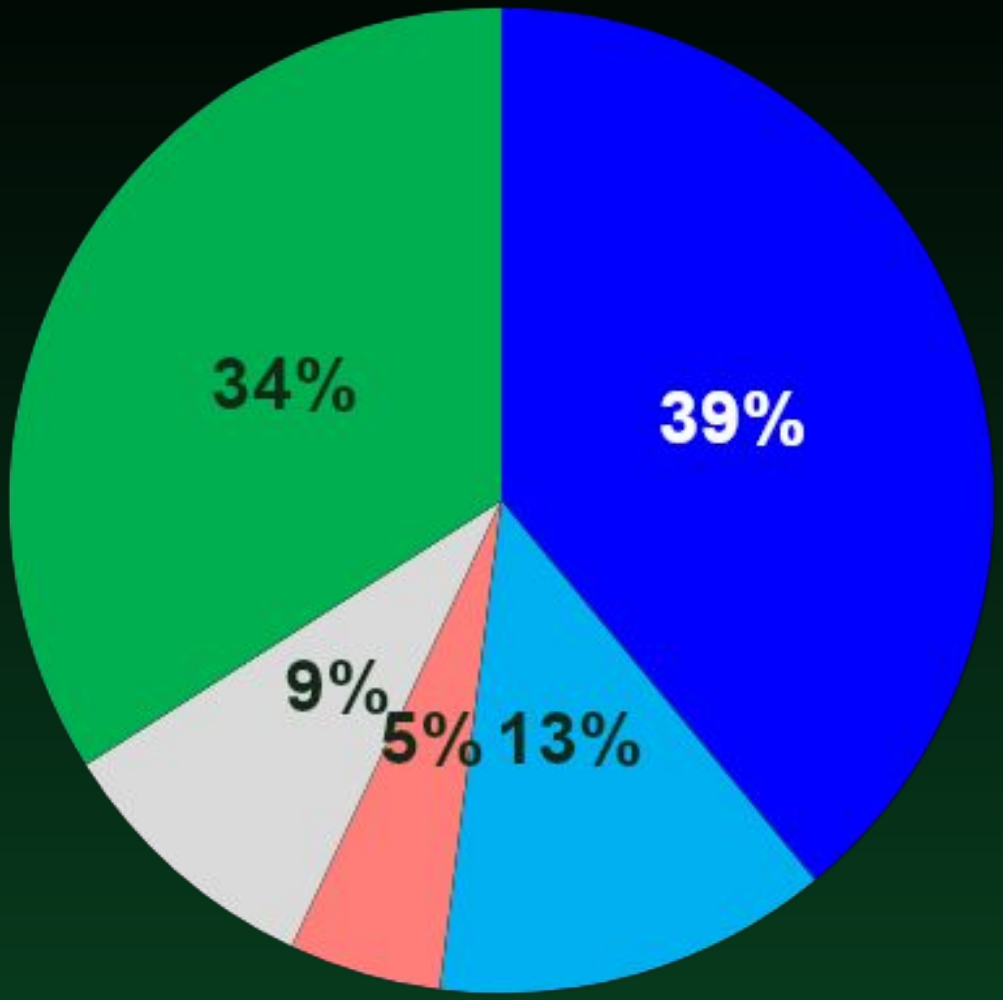
UTILITY OF ctDNA IN GIST

	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%

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

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Distribution of Primary Mutations (%)



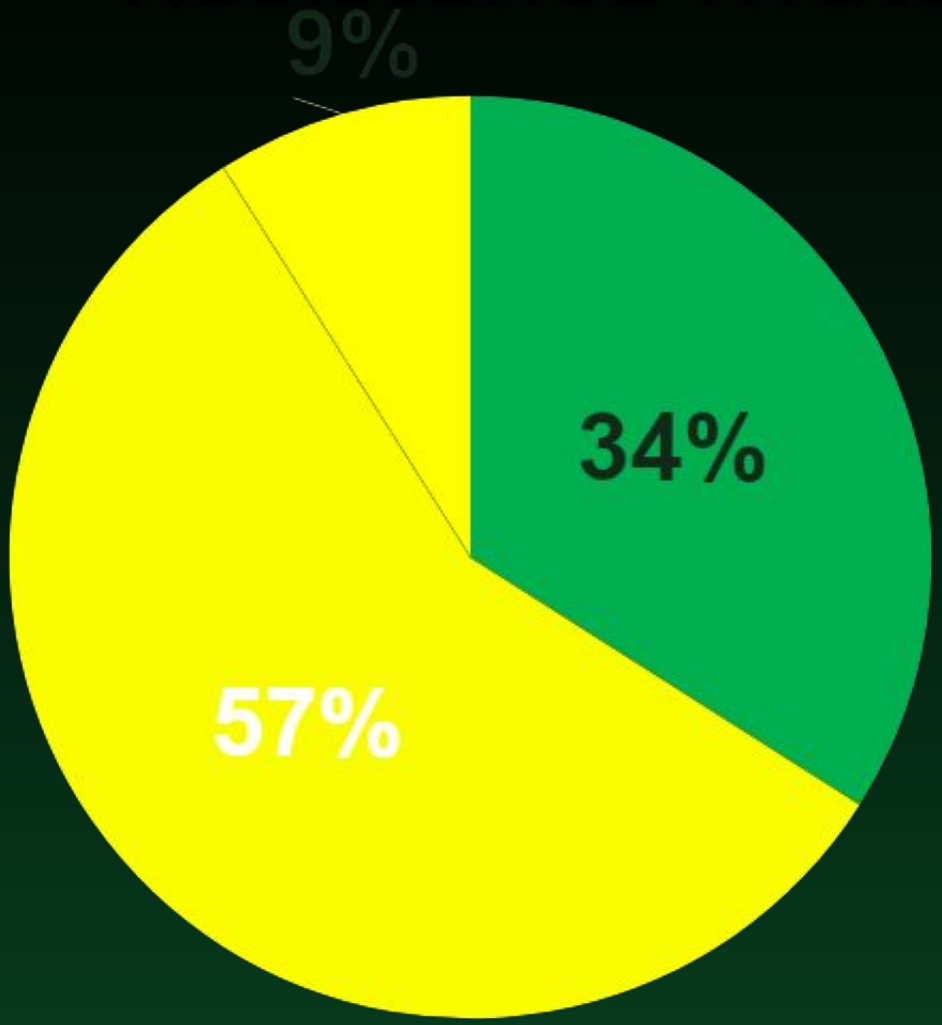
- Patients with mutation (n=162)
- KIT or PDGFR mutations (N=106)
- Not KIT/PDGFR (N=56)

- Kit exon 11
- KIT exon 9

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

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Resistance Mutations (%)

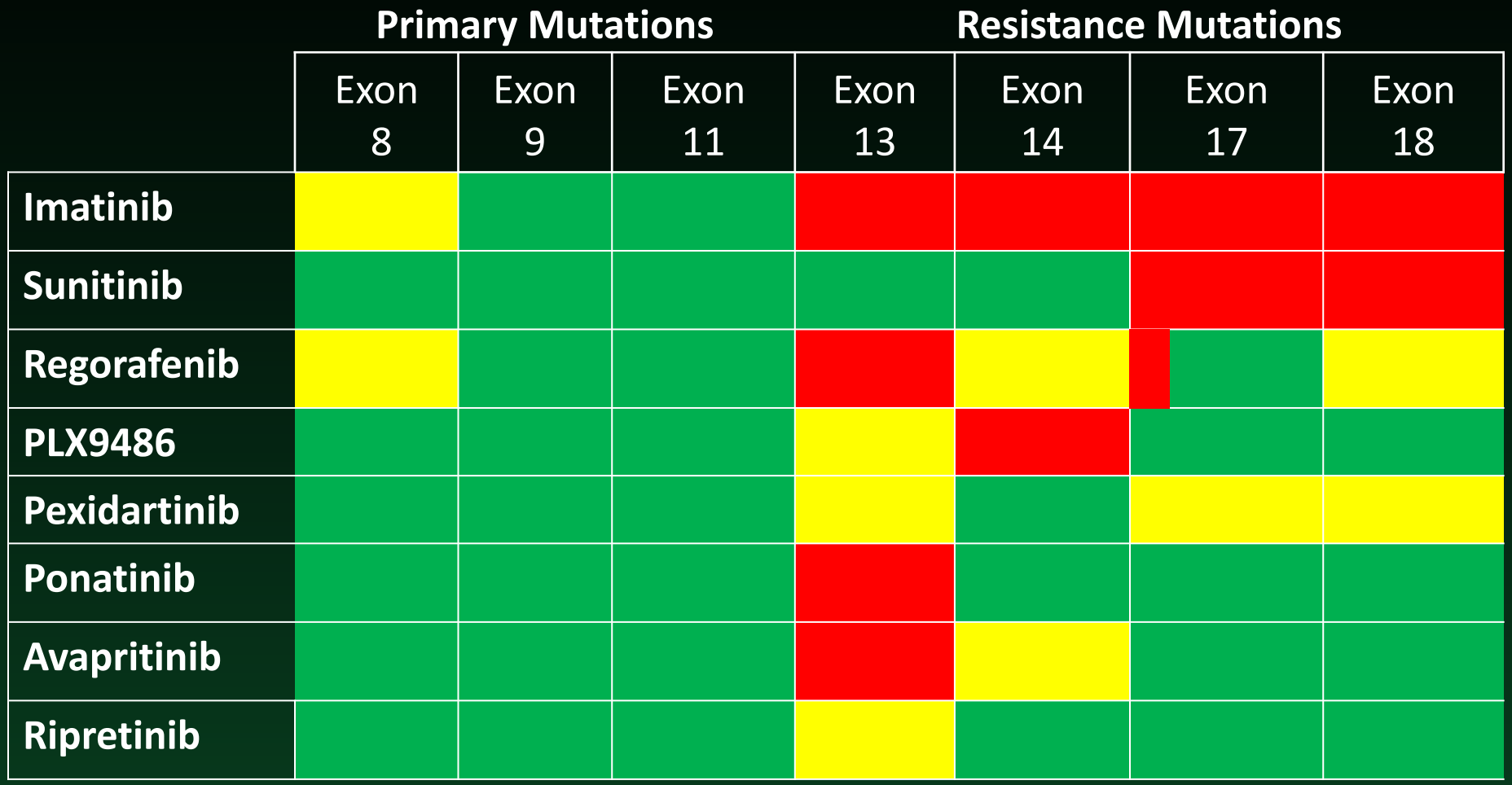


- Patients with KIT or PDGFR mutation (n=106)
- Other: Ras, NF-1, PI3K, TSC

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

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Differential Sensitivity to TKI



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

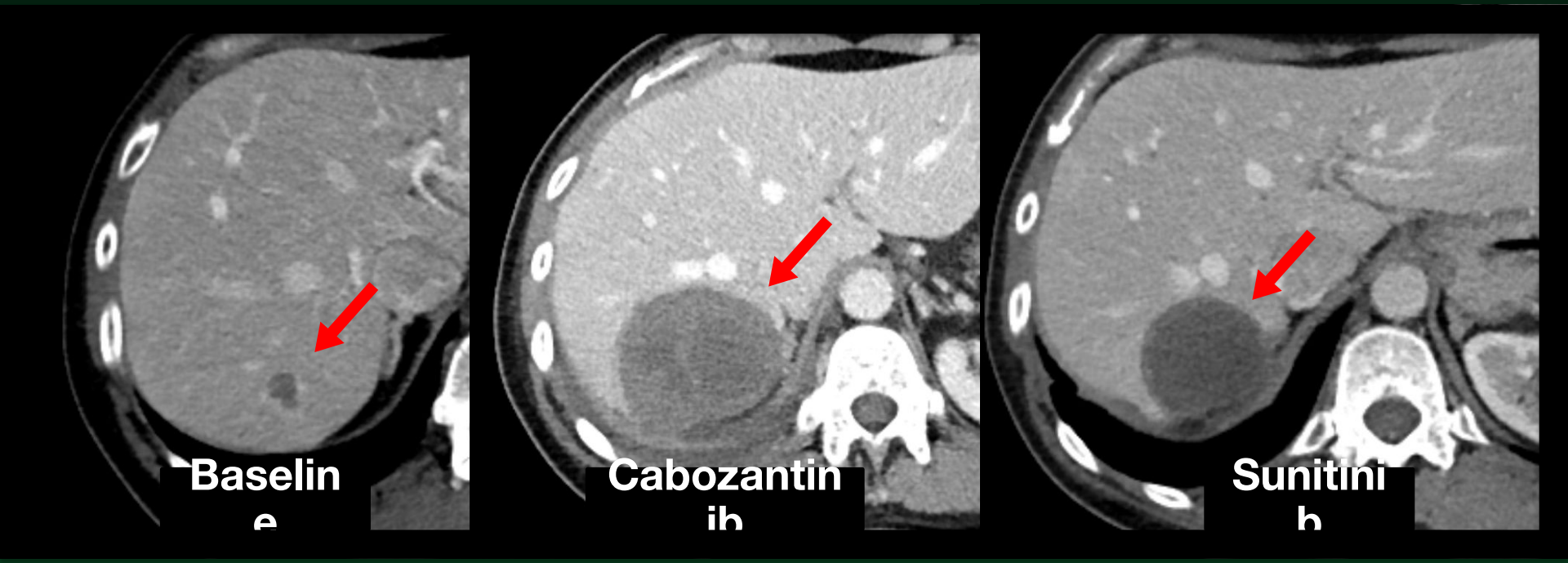
Trent, CTOS 2017

Serrano BJC 2018

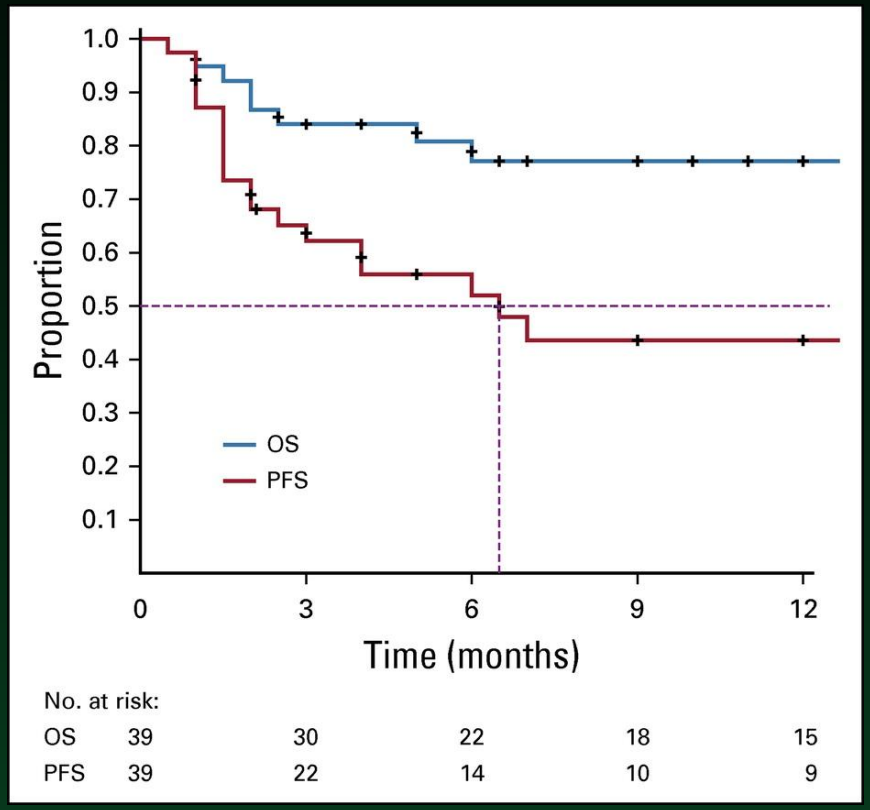
Gramza et al, Clinical Cancer Research 15:7510, 2009

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

- 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)



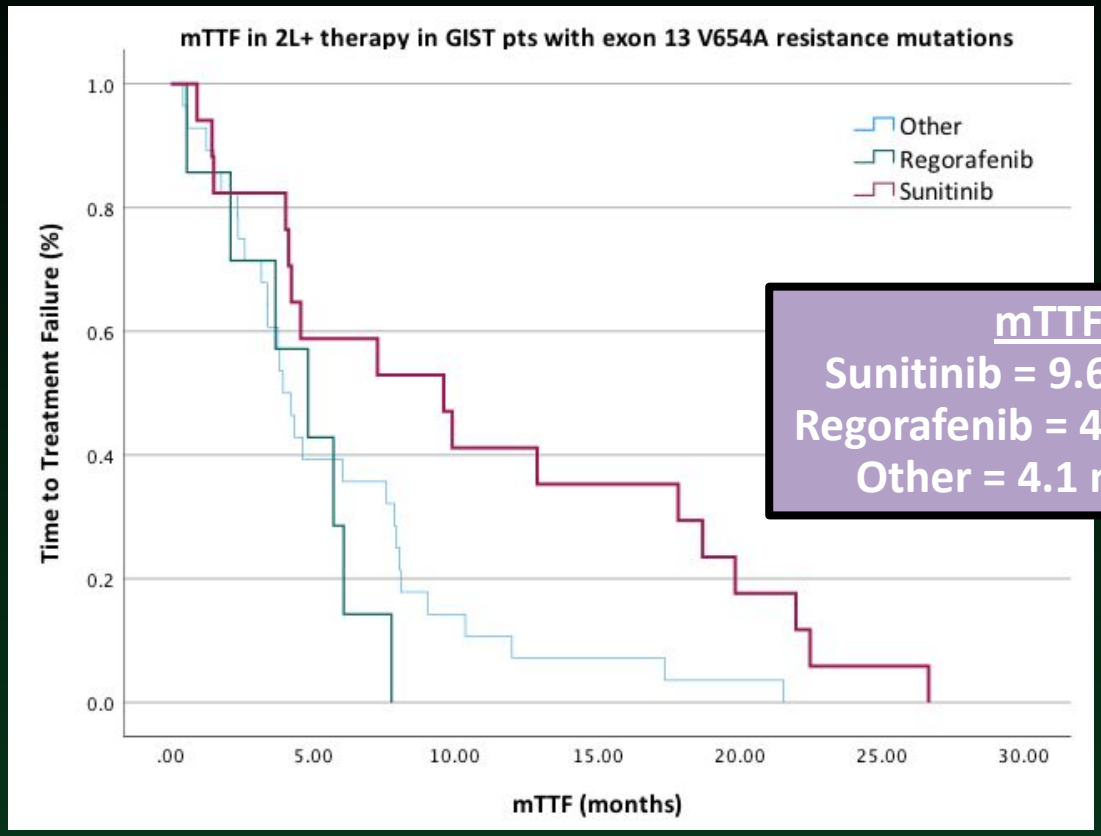
12 months from ctDNA testing (*n* = 39):

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

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

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

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

Bialick, Trent CTOS 2023

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

New Monotherapy Approaches

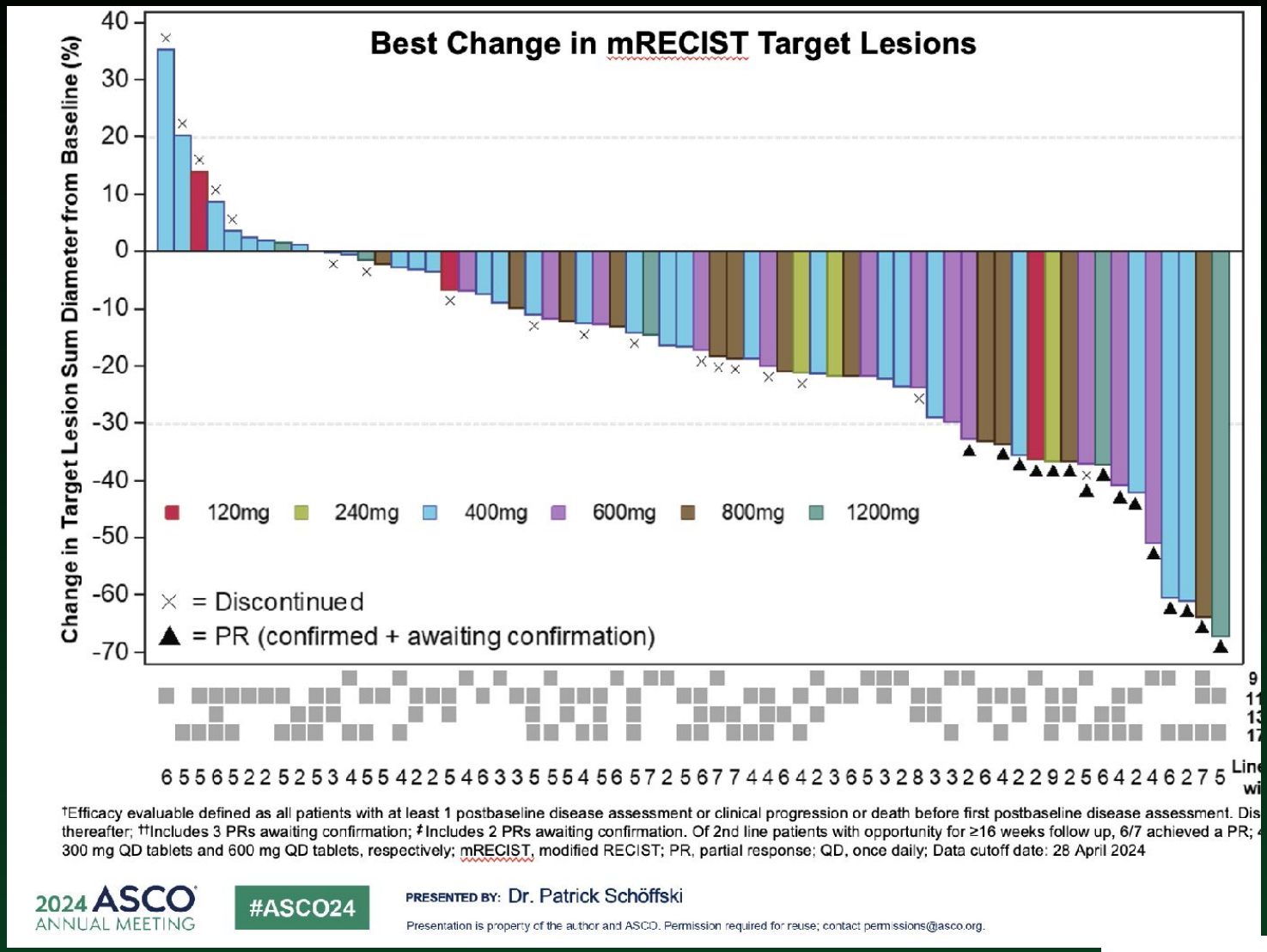
IDRX-42 (Velzatinib) Promising Activity

Next Generation KIT Inhibitor

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

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

IDRX-42 (Velzatinib) 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. Dis
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;
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

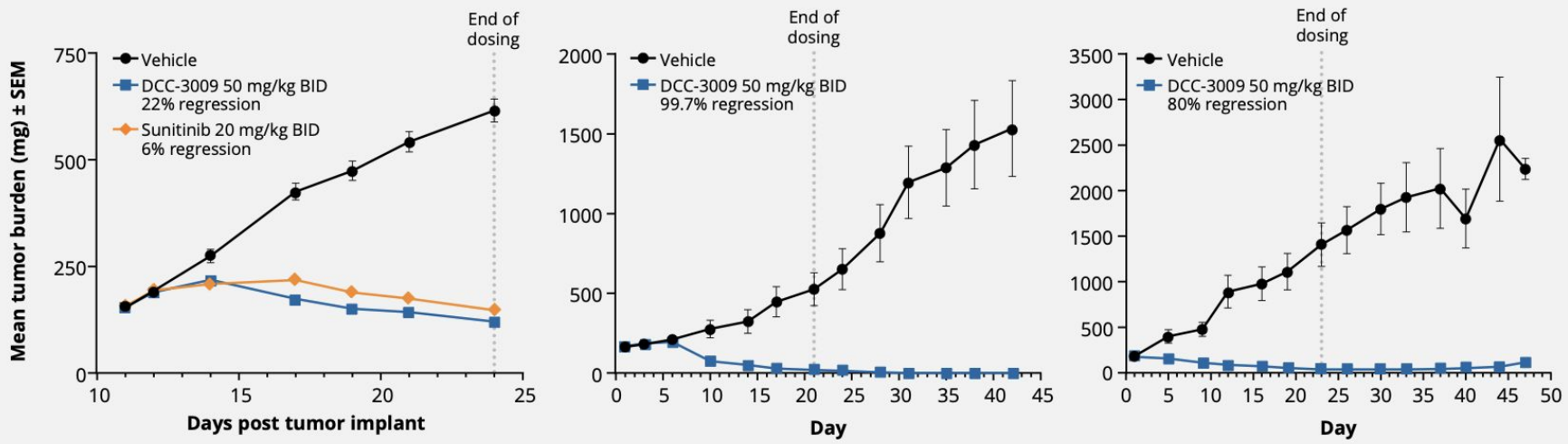
2024 ASCO ANNUAL MEETING

#ASCO24

PRESENTED BY: Dr. Patrick Schöffski

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

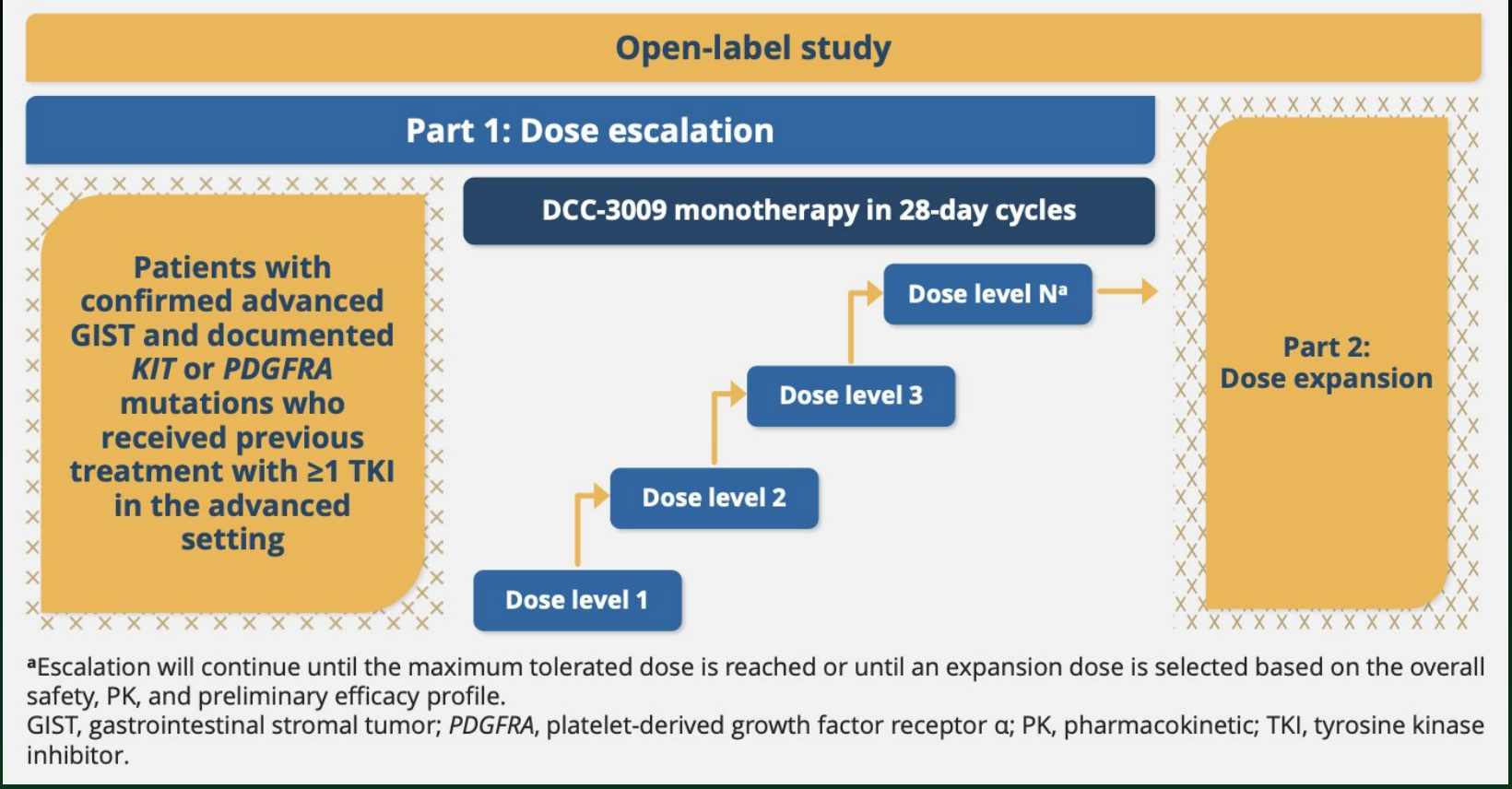
Robust antitumor activity of DCC-3009 in preclinical models



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.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Dose escalation study design



[a]Escalation will continue until the maximum tolerated dose is reached or until an expansion dose is selected based on the overall safety, PK, and preliminary efficacy profile.
GIST, gastrointestinal stromal tumor; *PDGFRA*, platelet-derived growth factor receptor α; PK, pharmacokinetic; TKI, tyrosine kinase inhibitor.

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

New Combination Therapy Approaches

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Common primary and secondary resistance mutations

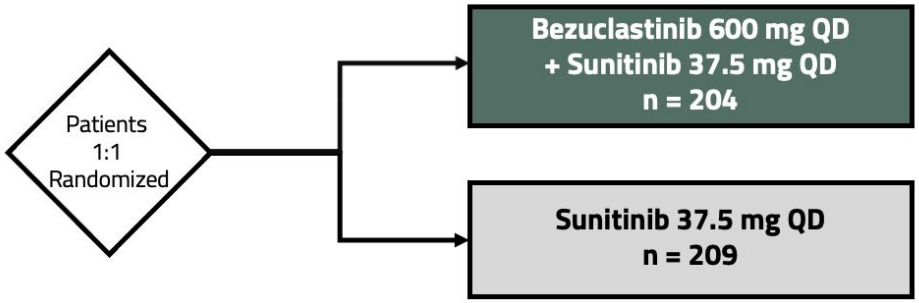
Target	Exon	Mutation	Bezu + Sunitinib	Imatinib	Sunitinib	NDE-Sunitinib	Regorafenib	Ripretinib	Velzatinib	NB003
cKIT WT	None	None	1	9	1	1	6	2	1	0.4
cKIT V560G	11	JMD	2	23	4	6	12	3	2	1
cKIT V654A	13	AP	4	1144	4	6	247	86	15	12
cKIT T670I	14	AP (gatekeeper)	4	3517	4	8	151	110	1455	38
cKIT D816H	17	AL	1	1990	353	473	174	3	29	97
cKIT D816V	17	AL	1	8971	308	364	1463	3	276	2334
cKIT D820Y	17	AL	6	70	148	152	19	3	1	2
cKIT N822K	17	AL	2	76	308	353	30	3	3	7
cKIT Y823D	17	AL	14	190	121	147	10	2	1	3

Table is based on preclinical data.

References. 1. Wagner AJ, et al. Connective Tissue Oncology Society (CTOS) annual meeting. Vancouver, Canada. 2022. 2. Wagner AJ, et al. JAMA Oncol 2021;7(9):1343–1350. 3. Guarnieri A, et al. American Association for Cancer Research (AACR) annual meeting. 2022. 4. Guarnieri A, et al. American Association for Cancer Research (AACR) annual meeting. 2022. 5. Wagner A, et al. ASCO annual meeting. Chicago, 2024.

Peak is a Global, Randomized, Open-Label Phase 3 Study

Evaluating the efficacy and safety of bezuclastinib + sunitinib vs sunitinib as 2L treatment (NCT05208047)



Crossover allowed following BICR confirmed PD

Patient Eligibility

- Age ≥ 18 years
- Histologically confirmed GIST with at least 1 measurable lesion per mRECIST v1.1
- Locally advanced, unresectable or metastatic GIST
- Documented disease progression on or intolerance to imatinib

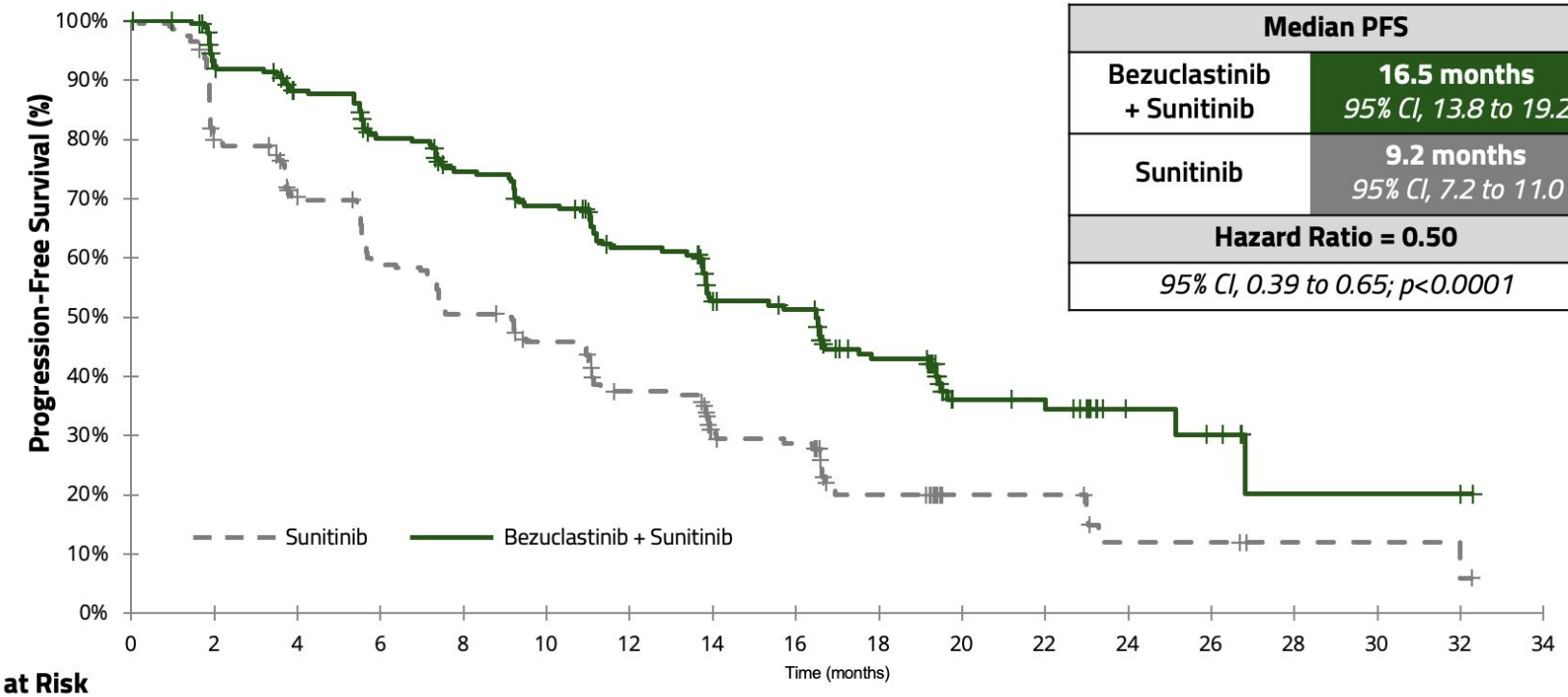
Primary Endpoint	• Progression Free Survival per BICR
Key Secondary Endpoints	• Objective Response Rate per BICR • Overall Survival
Secondary Endpoints	• Progression Free Survival per Investigator • Disease Control Rate • Time to Response • Duration of Response

Data cut-off as of 30 September 2025

Statistical assumptions: median PFS of 8 months for sunitinib and 12 months for bezuclastinib + sunitinib.

2L, second-line therapy; BICR, blinded independent central review; GIST, gastrointestinal stromal tumor; mRECIST v1.1, modified response evaluation criteria in solid tumors; criteria used to assess treatment response in GISTs; PD, progressive disease; QD, quaque die (once daily).

Bezuclastinib + Sunitinib Reduction in Risk of Progression or Death



Median PFS	
Bezuclastinib + Sunitinib	**16.5 months** *95% CI, 13.8 to 19.2*
Sunitinib	**9.2 months** *95% CI, 7.2 to 11.0*
Hazard Ratio = 0.50	
95% CI, 0.39 to 0.65; p<0.0001	

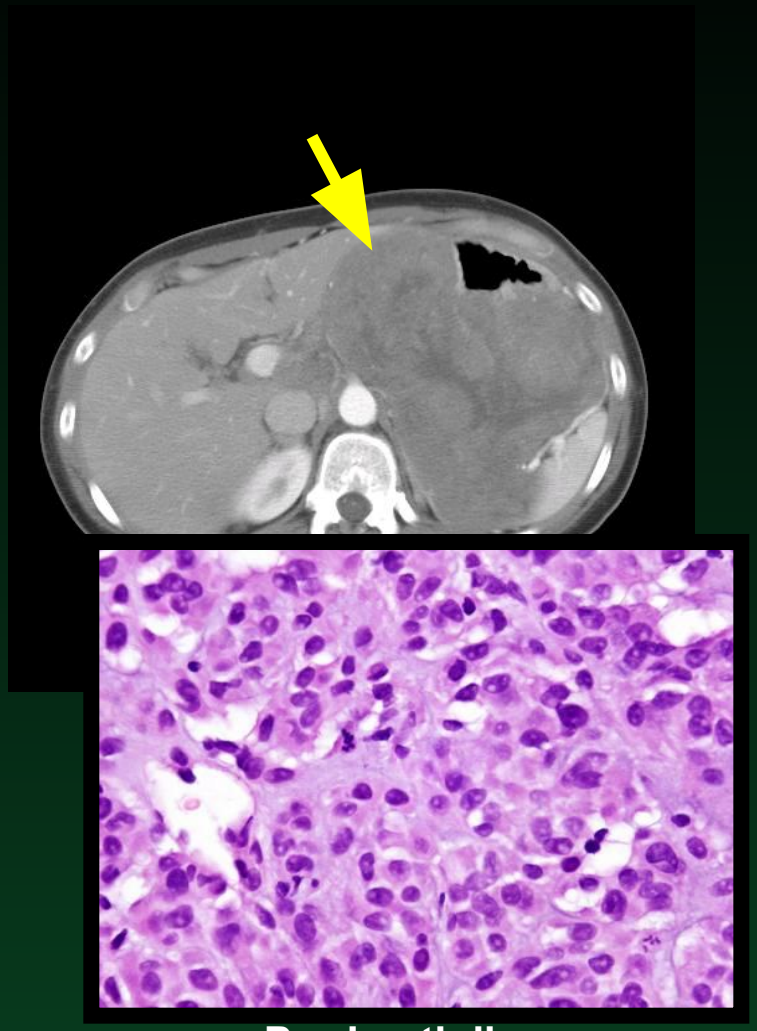
Patients at Risk

Bezuclastinib + Sunitinib	204	180	166	146	130	119	102	76	72	51	24	23	8	6	2	2	2	0
Sunitinib	209	161	137	113	97	85	64	39	35	19	9	9	4	4	2	2	2	0

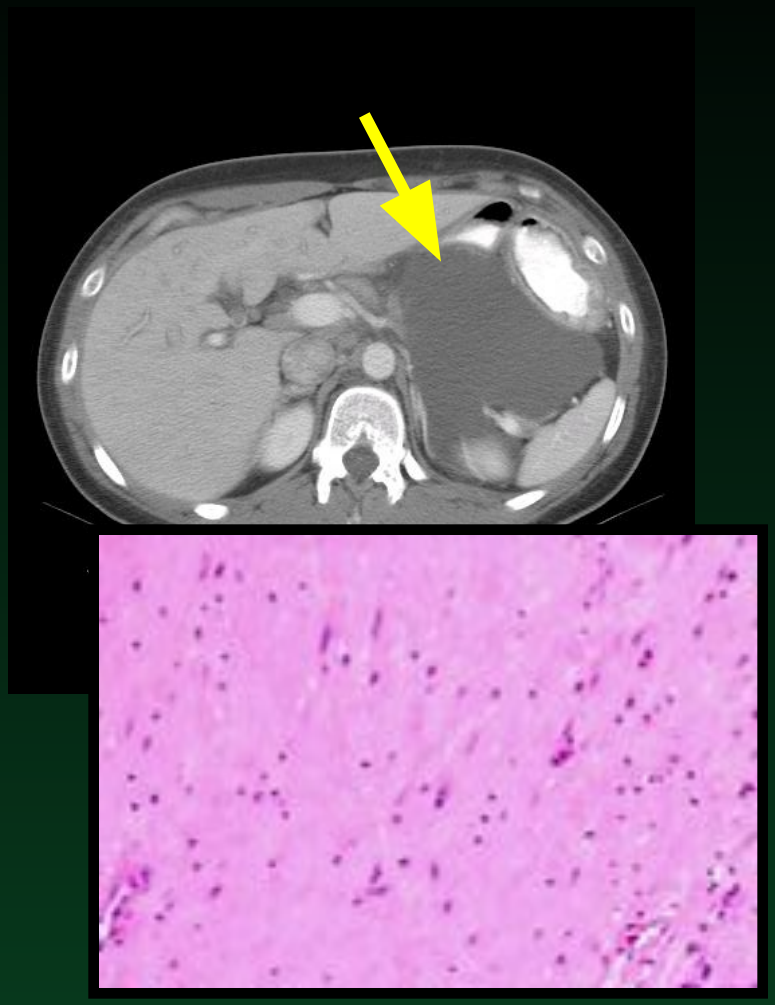
Data cut-off as of 30 September 2025

CI, confidence interval; PFS, Progression-Free Survival.

Efficacy of Imatinib



Pre-Imatinib

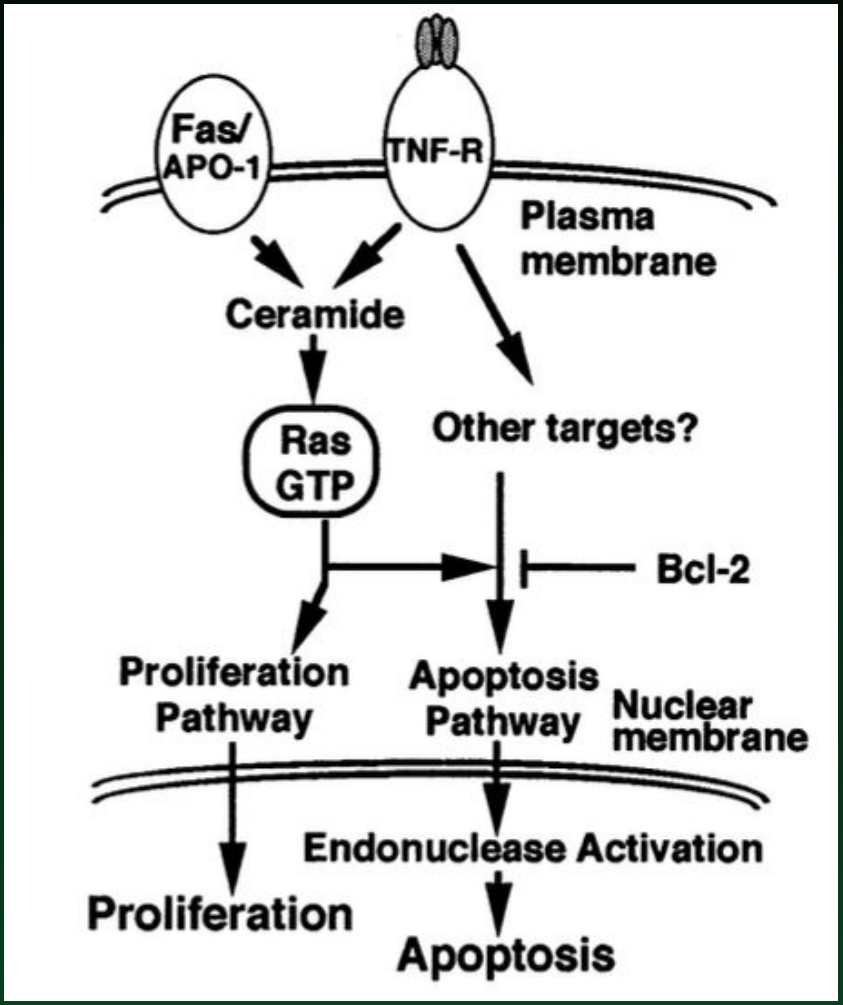


Post-Imatinib (8 weeks therapy)

Tibes, Kurzrock and Trent, Annu Rev Pharmacol Toxicol. 2005:45:357-84

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Induction of Apoptosis by Recepeptor Signaling



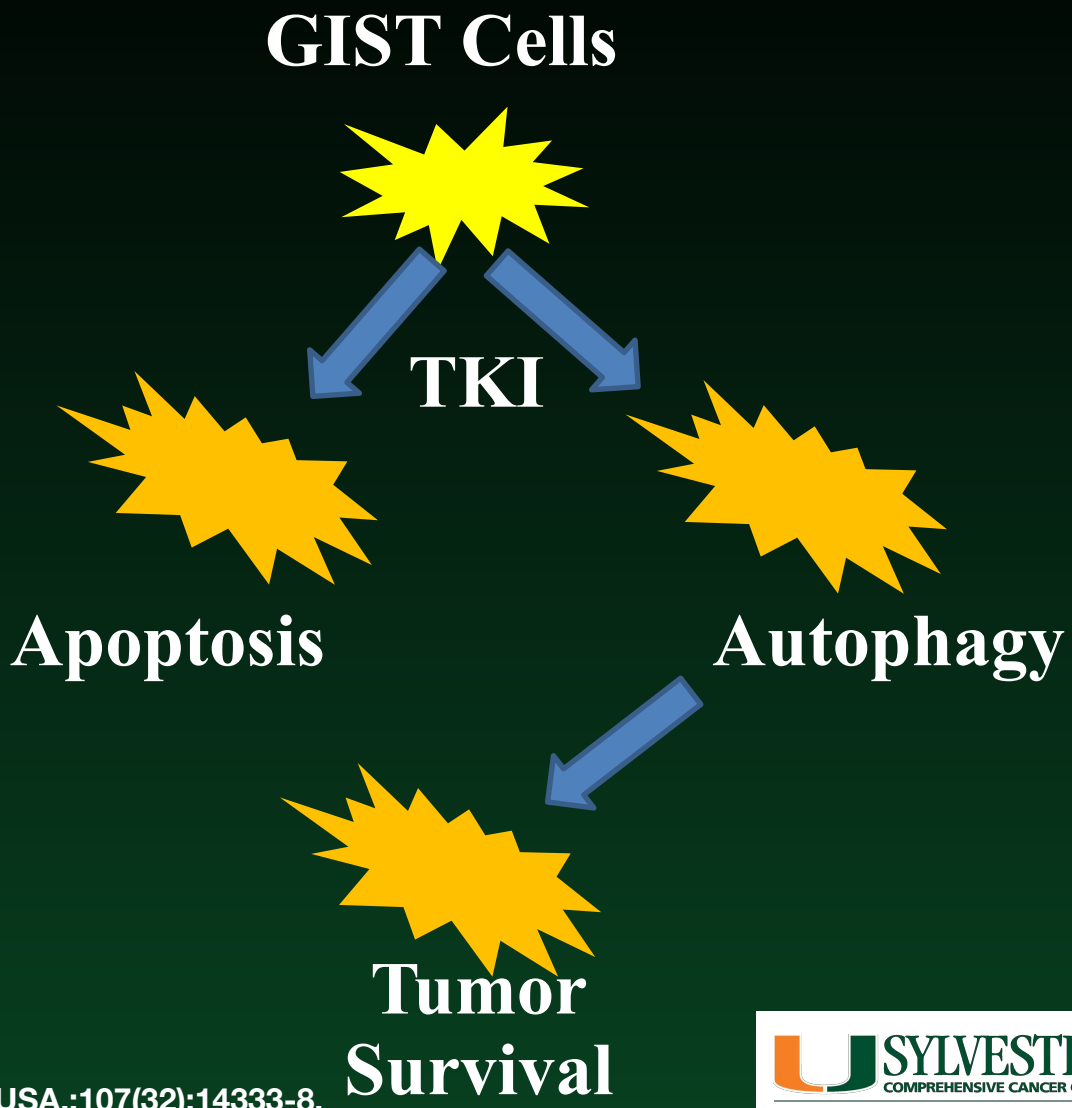
Trent, et al TheEMBOJournalvol.15no.17pp.4497-4505

SYLVESTER
COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Hypotheses

GIST Cells survive by Autophagy

Autophagy inhibitors will enhance apoptosis

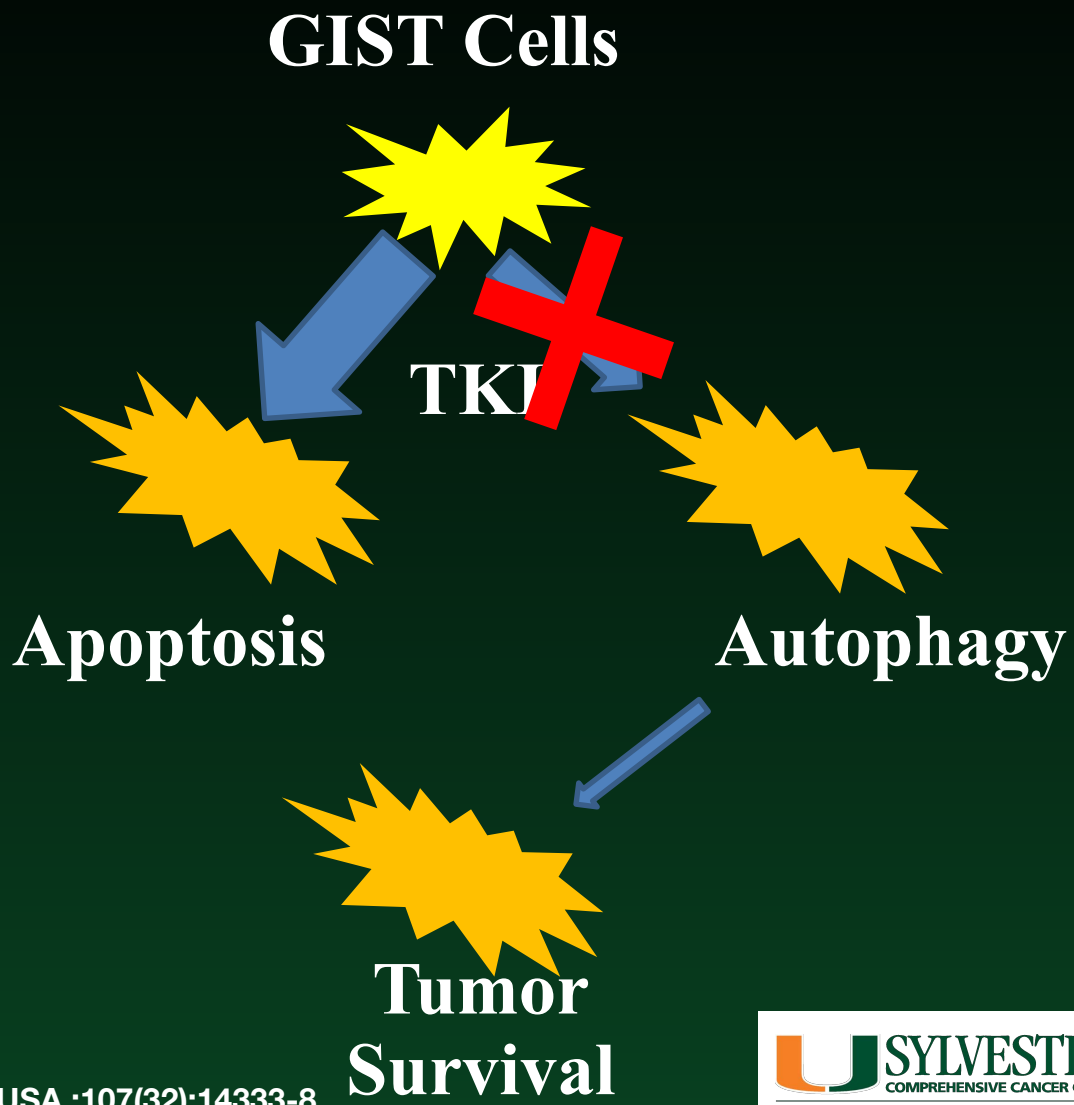


Gupta A, Trent J, Rubin BP. Proc Natl Acad Sci USA.;107(32):14333-8.

Hypotheses

GIST Cells survive by Autophagy

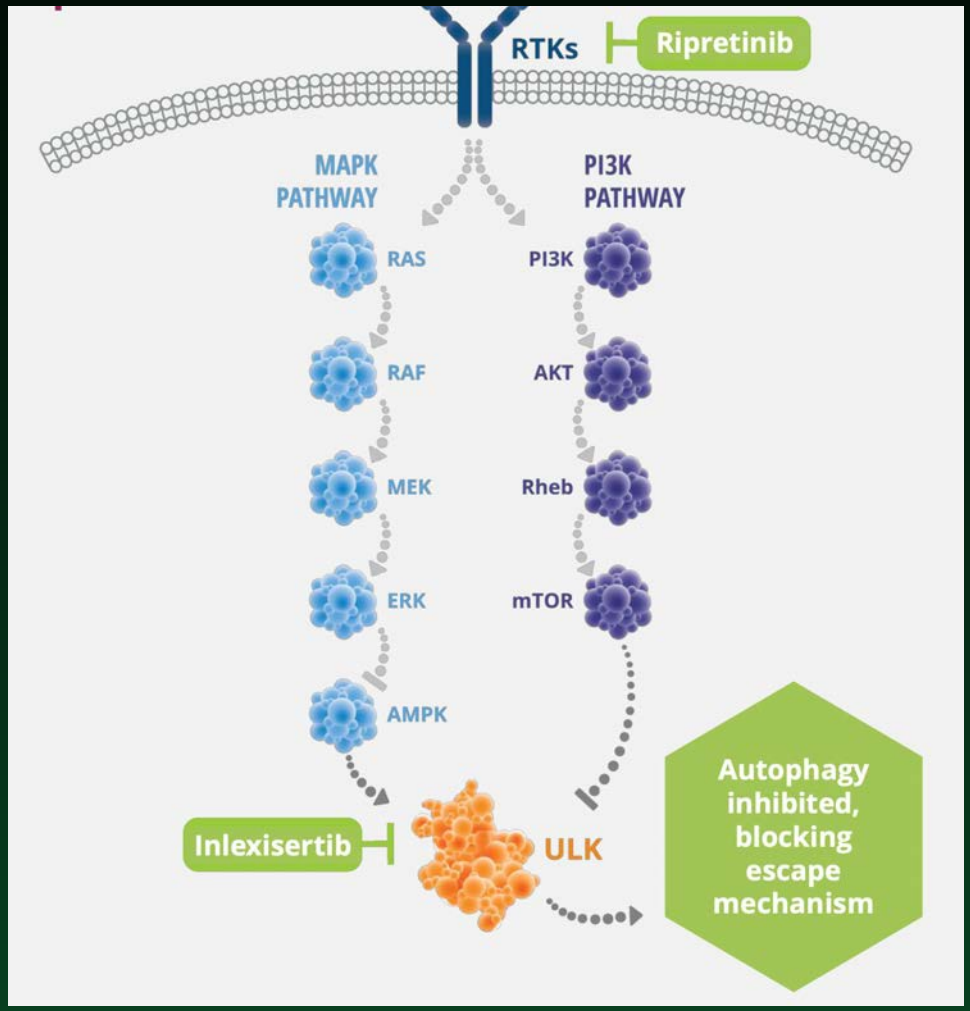
Autophagy inhibitors will enhance apoptosis



Gupta A, Trent J, Rubin BP. Proc Natl Acad Sci USA.;107(32):14333-8.

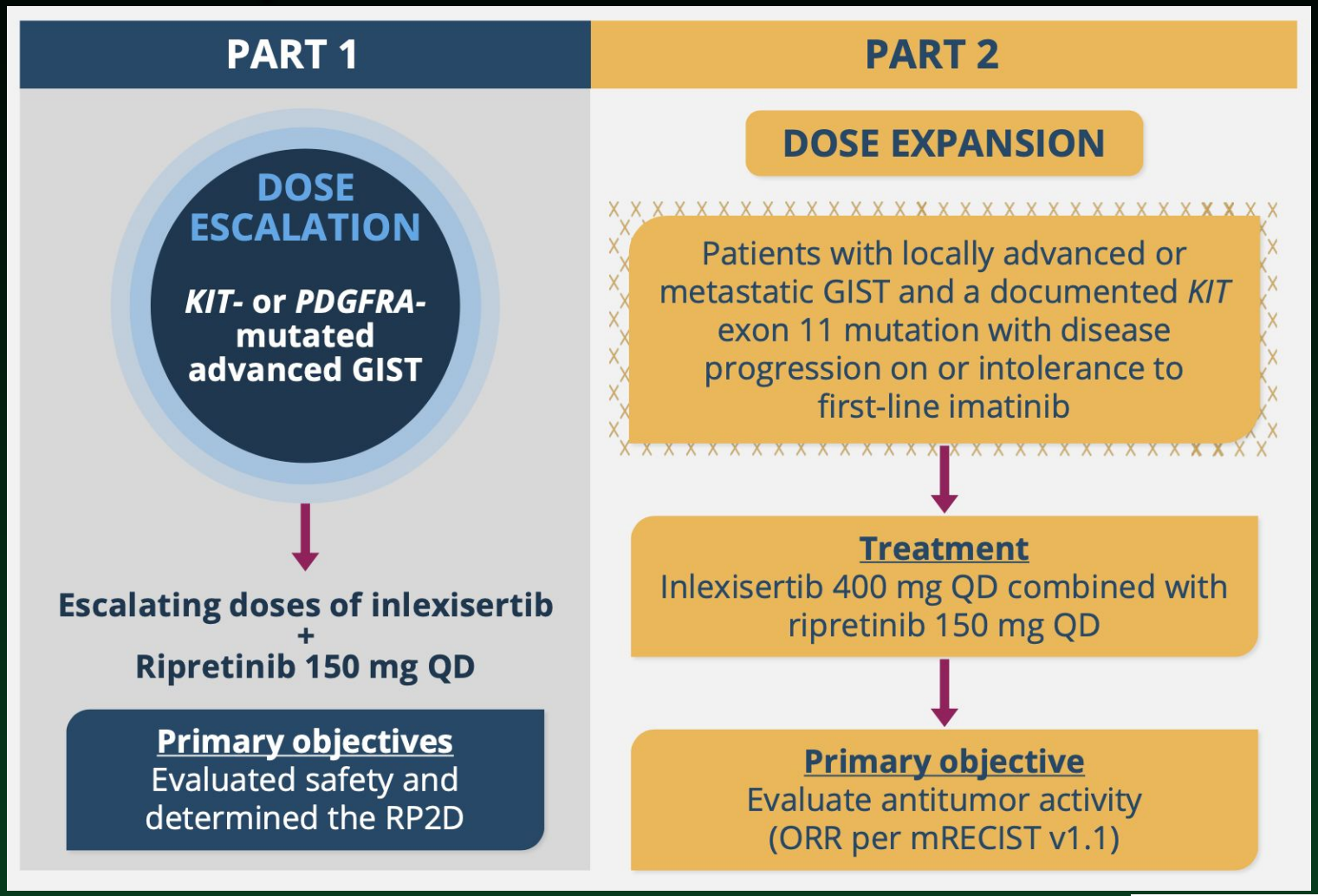
Ripretinib + DCC-3116

DCC-3116 inhibits autophagy driven by ULK1/2 in response to RTK inhibition by ripretinib



SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Ripretinib + DCC-3116



SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Clinical Trials for GIST Patients

- **Phase 1 Studies**
  - Ripretinib + DCC-3116 (Autophagy inhibitor) – 2nd line
  - DCC-3009 (new KIT inhibitor) – any line
  - Imatinib + Ziftomenib (Oral Menin Inhibitor)- 1st line
  - PRMT5i (MTAP deleted GIST) – planned, any line
- **Phase 2**
  - ctDNA-guided therapy for GIST patients (IntellliGIST) – any line
    - any line prior therapy
    - must have exon 13/14 or 17/18 resistance mutation
    - ctDNA testing provided
  - Imatinib + KQB198 (SOS inhibitor) vs Imatinib – 1st line
- **Phase 3**
  - IDRX-42 (Velzatinib) vs Imatinib – 1st line
  - IDRX-42 (Velzatinib) vs Sunitinib – 2nd line

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Conclusions

- Mutation testing is necessary for optimal treatment outcome
- ctDNA testing at each instance of progression
- Many new clinical trials on the horizon
- 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
UNIVERSITY OF MIAMI HEALTH SYSTEM

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
  - Ty Subhawong
  - Francesco Alessandrino
  - Felipe de Souza
  - Fabiano Cardosa
- Nurse Practitioner
  - Morgan Smith
  - Solange Sierra
  - Ali Naveda
  - Zulay Chang
- Orthopedic Oncology
  - Fran Hornicek
  - 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

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

THANK YOU!

SYLVESTER
COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Emerging Strategies for the Treatment of Gastrointestinal Stromal Tumor (GIST)

FLASCO Rare Cancers 2026

Jon Trent, MD, PhD

Professor of Medicine
Director, Bone and Soft-tissue Sarcoma
Associate Director, Clinical Research
The University of Miami, Sylvester Comprehensive Cancer Center

jtrent@med.miami.edu

@JTrentMDPhD

SYLVESTER COMPREHENSIVE CANCER CENTER

UNIVERSITY OF MIAMI HEALTH SYSTEM