UC San Diego Health

The Genomics of *KIT/PDGFRA* Wild-type GIST & Emerging Approaches for SDH-Deficient GIST

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Program Director, SOAS T32 Training Program | Department of Surgery & Moores Cancer Center


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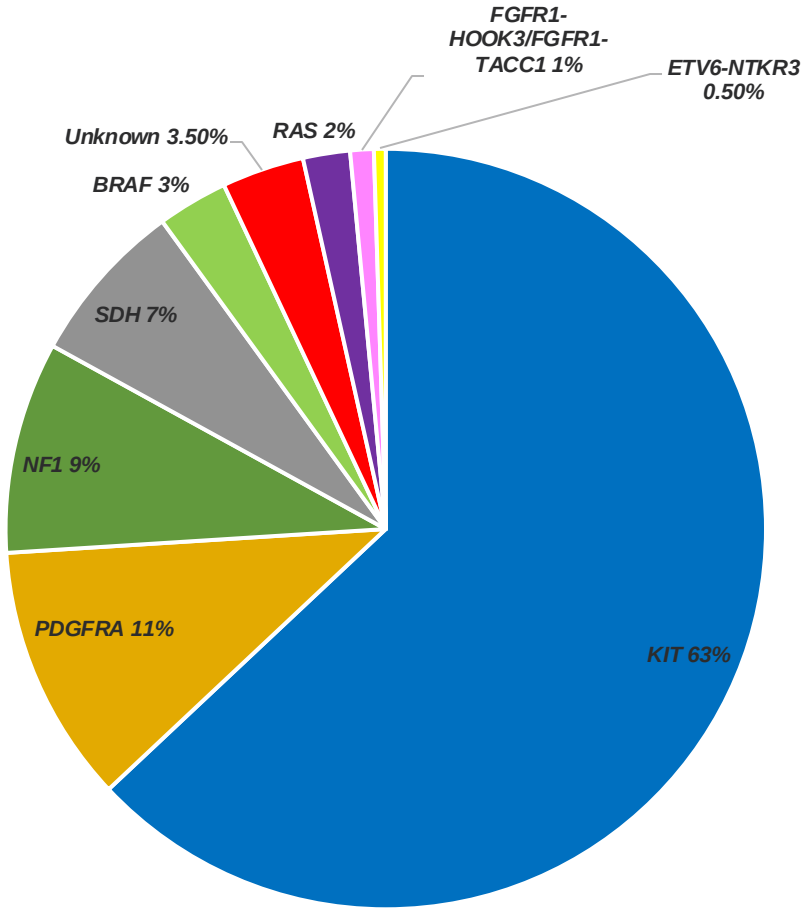
Evolution of GIST Genomics



Shi *et al., J Trans Med*. 2016

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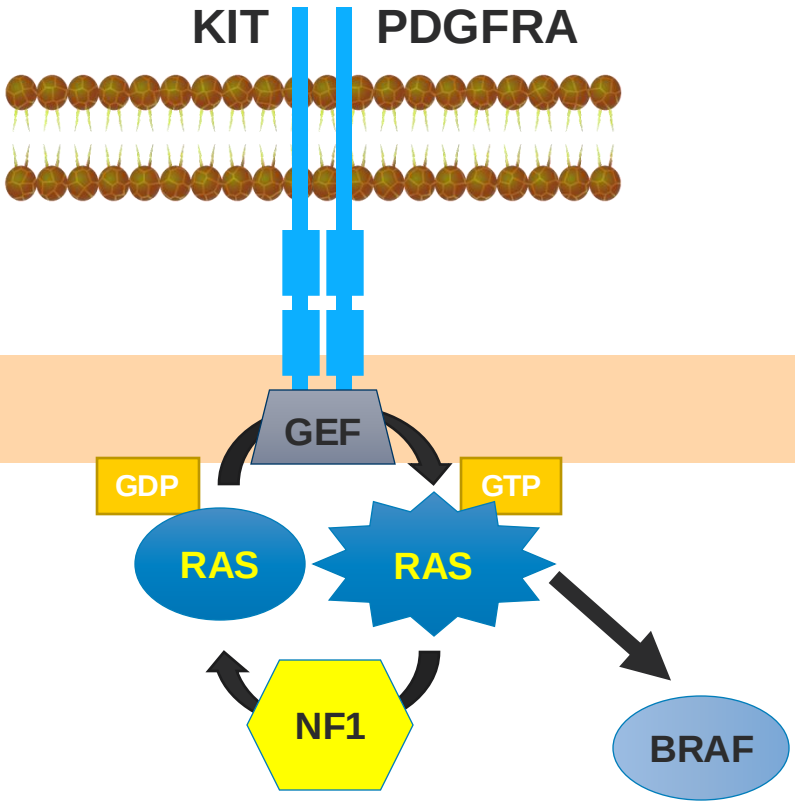

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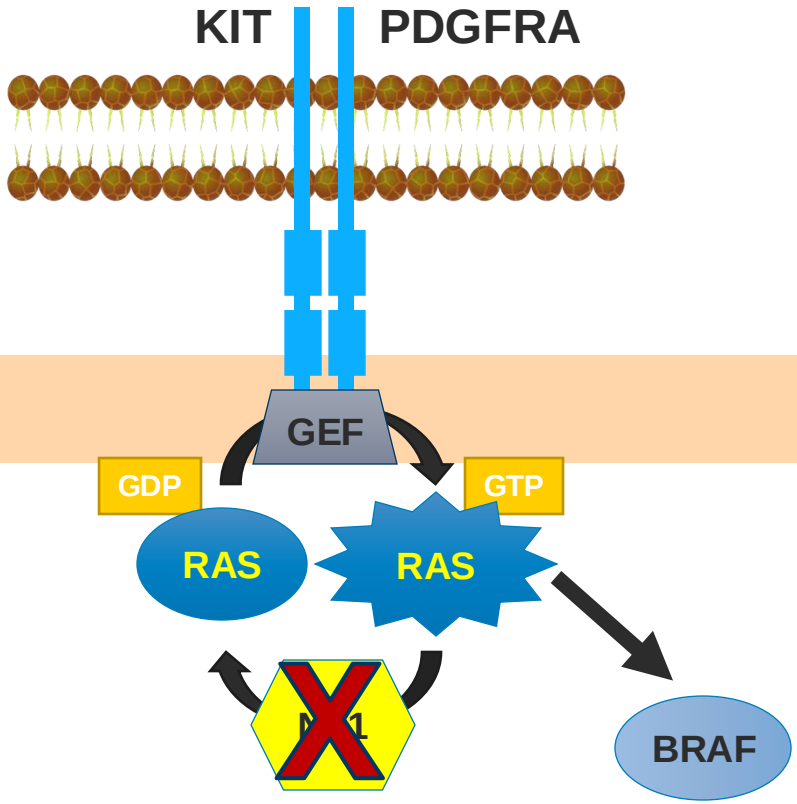
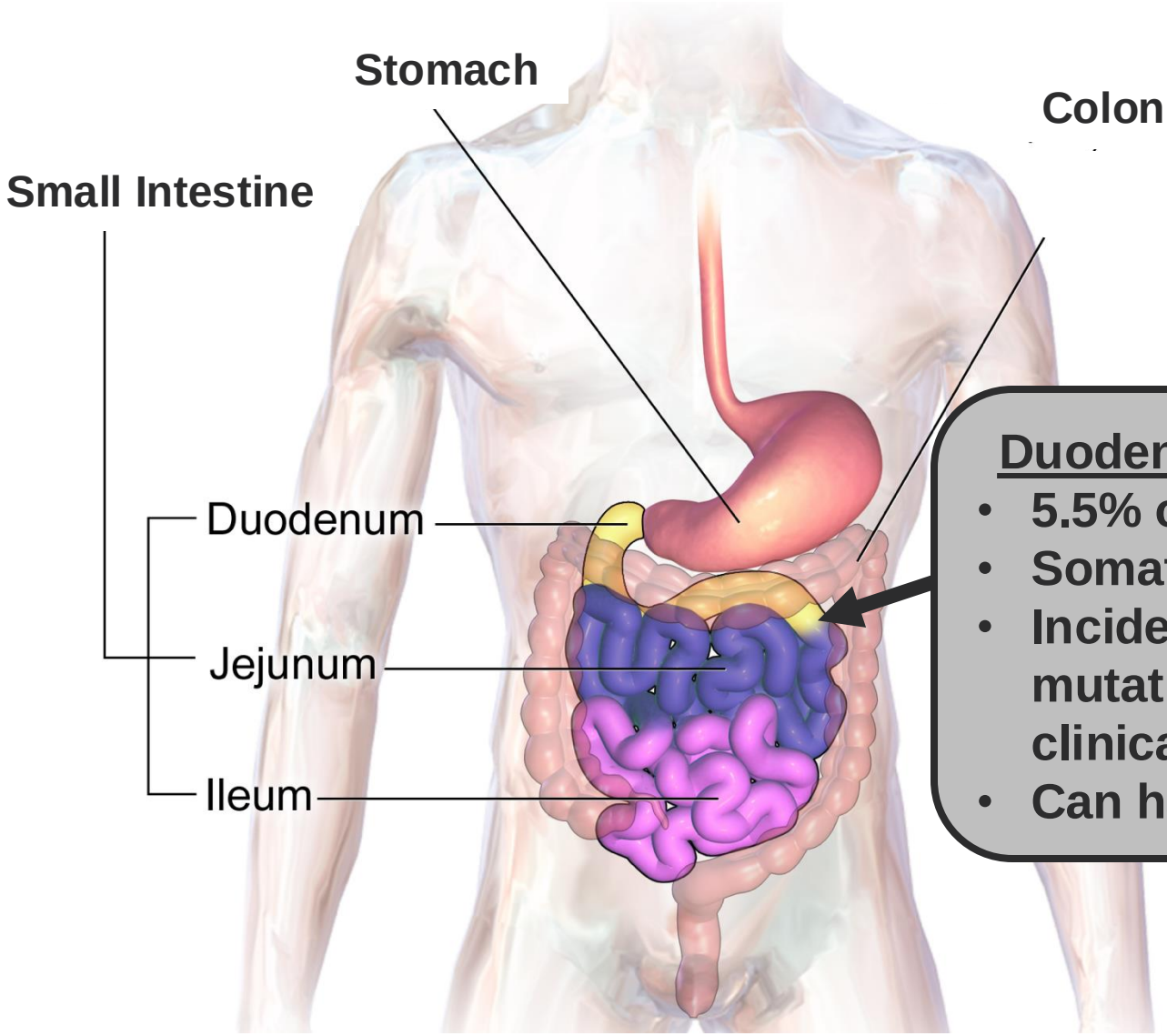


Germline NF1 Mutant GIST

1. Often multifocal small intestine GISTs associated with Neurofibromatosis type 1 (NF-1)
    - Hereditary
    - 1.5% of GISTs associated with NF-1
    - Often indolent
    - May or may not respond to imatinib
    - No drugs to target NF1

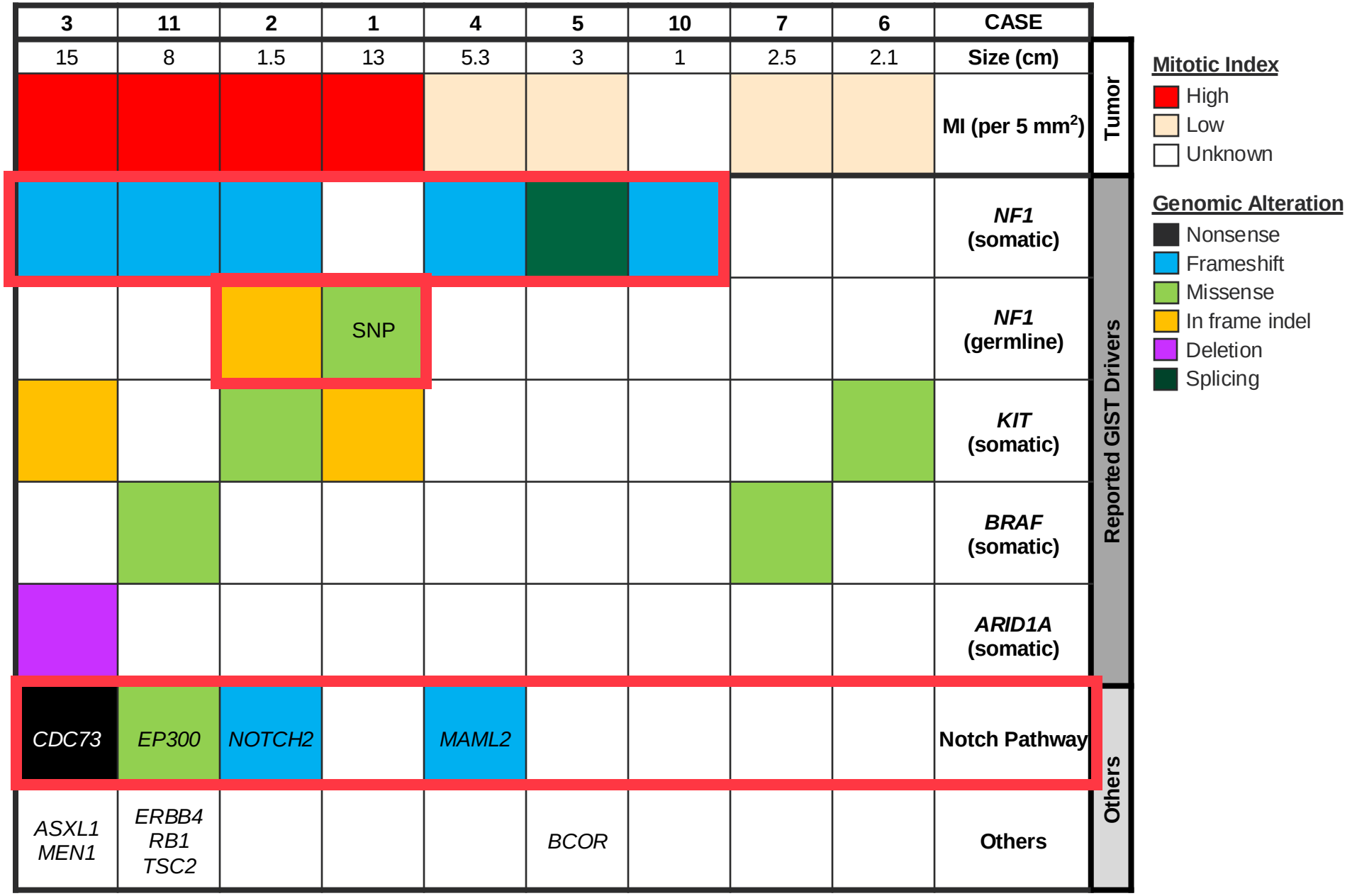
2. Somatic (not inherited) *NF1* mutant small bowel GIST was reported in 2015 in absence of a germline *NF1* mutation (Belinsky *et al.*, *BMC Cancer*, 2015).

Somatic *NF1*-mutant GIST



Duodenal-Jejunal Flexure (DJF)

- **5.5% of GISTs**
- **Somatic only *NF1* mutations**
- **Incidental germline *NF1* mutations even without clinical NF-1**
- **Can have *NF1* + *KIT* mutations**


3
11
2
1
4
5
10
7
6
CASE
15
8
1.5
13
5.3
3
1
2.5
2.1
Size (cm)
MI (per 5 mm2)
Tumor
NF1 (somatic)
NF1 (germline)
SNP
KIT (somatic)
BRAF (somatic)
ARID1A (somatic)
Reported GIST Drivers
CDC73
EP300
NOTCH2
MAML2
Notch Pathway
ASXL1
MEN1
ERBB4
RB1
TSC2
BCOR
Others
Others
Mitotic Index
High
Low
Unknown
Genomic Alteration
Nonsense
Frameshift
Missense
In frame indel
Deletion
Splicing

NF1 Summary

- Duodenal-Jejunal Flexure (DJF) or Ligament of Treitz GISTs frequently possess *NF1* alterations (somatic and/or germline), which occur even in the absence of clinical NF-1
- This represents a previously unappreciated presentation of clinical NF-1.

Solitary GIST arising at the DJF may be a biomarker for clinically occult NF-1 even if single gene testing reveals a *KIT* mutation, or *BRAF* mutations.

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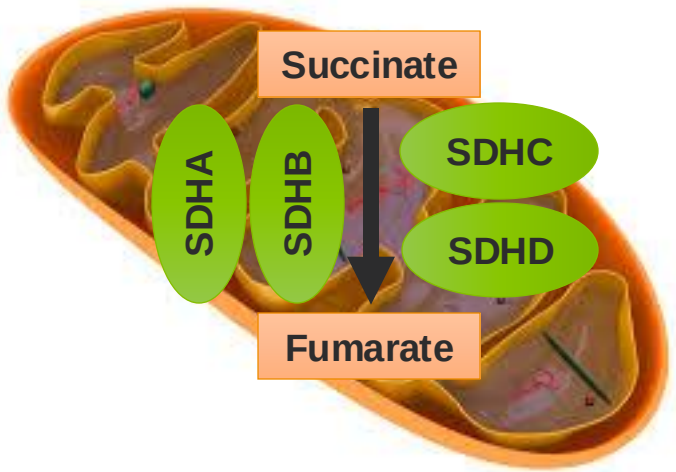

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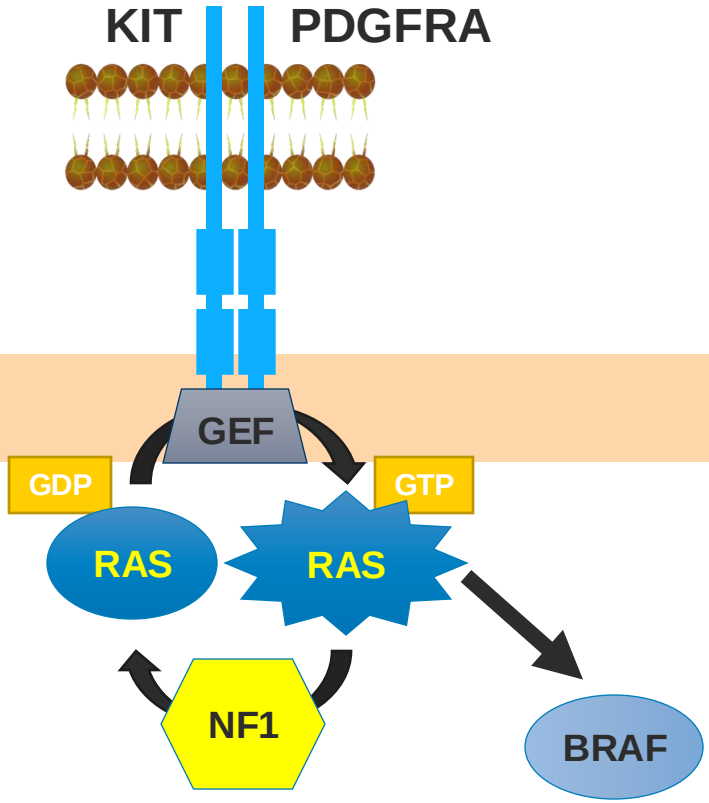
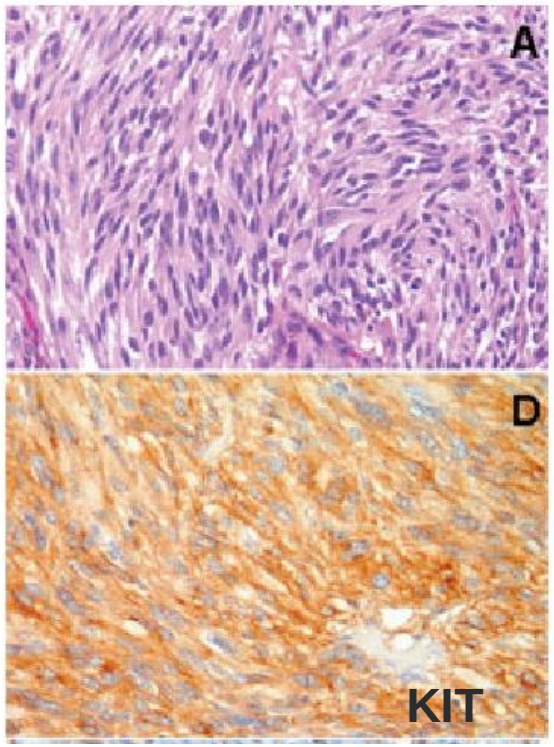


BRAF ^{V600E} mutant

TABLE 1. Clinical and Pathologic Findings in BRAF mutated GIST patients

	Age/Sex	Primary Tumor Size (cm)	Primary Tumor Site	MF/50 HPF	Stage at presentation	CD117	PTEN	P16	LFU/mo
1[a]	52/F	10	SB	90	Periton Mets	P	P	N	DOD/18
2	55/F	10	SB	5	Primary	P	NA	NA	NED/9
3	49/F	9	SB	50	Primary	P	P	P	NED/13



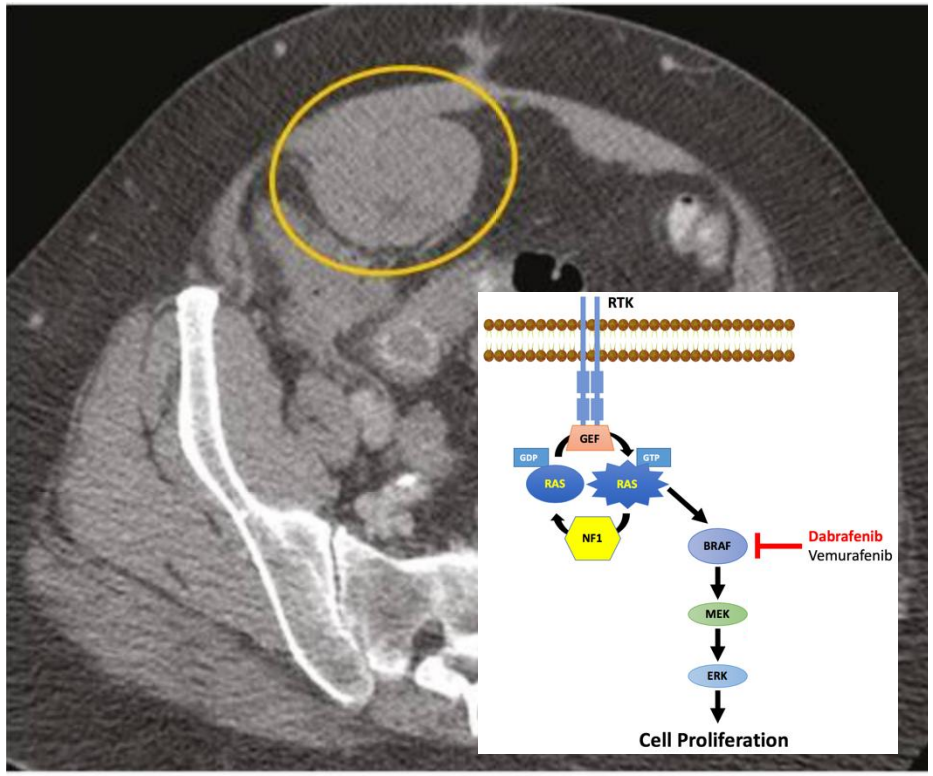
- **Small bowel**
- **KIT-positive IHC**
- **Variable behavior**

Agaram NP, Genes Chromosomes and Cancer 2008

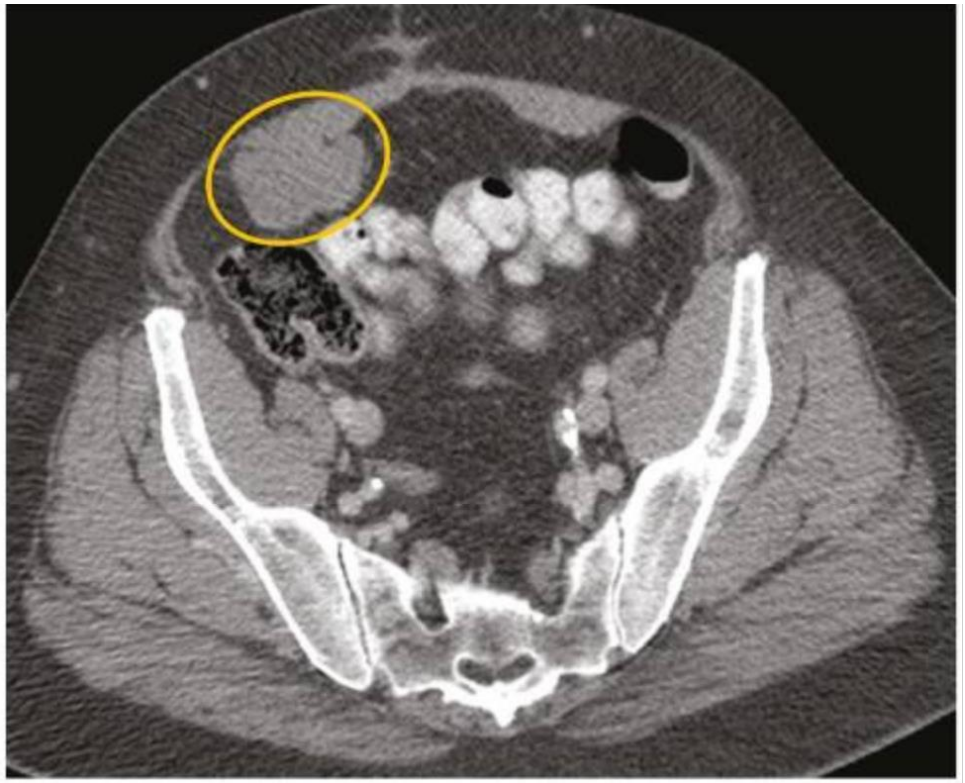
BRAF ^{V600E} mutant GIST

FEBRUARY 2007 (WEEK 0)

- Treatment with dabrafenib



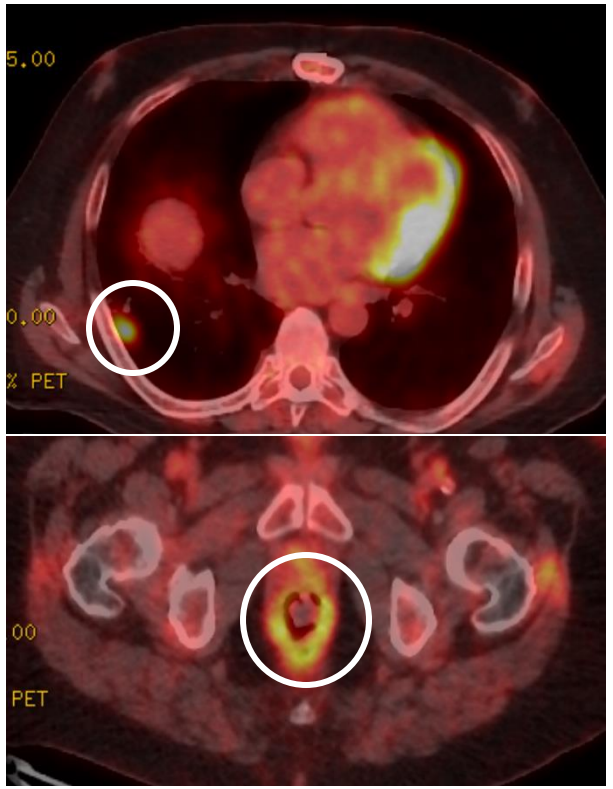
MARCH 2008 (WEEK 24)

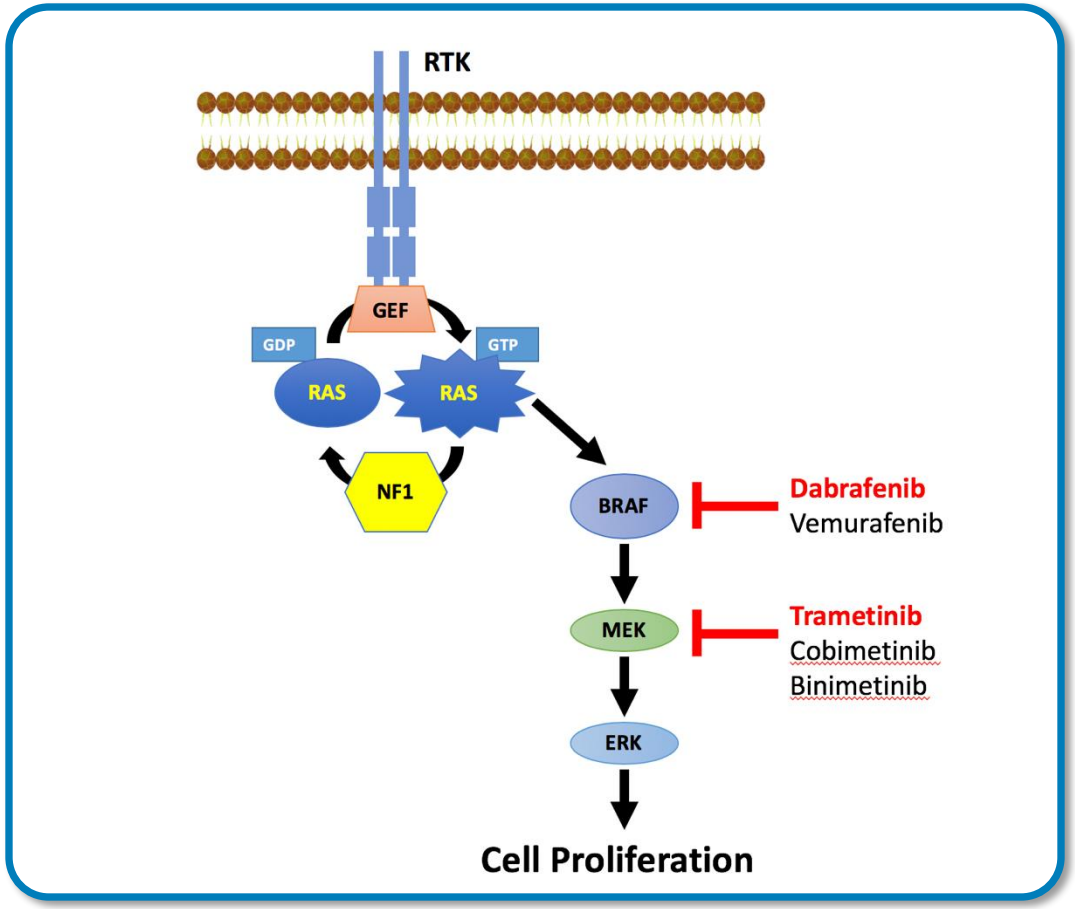


Falchook *et al., Oncotarget* 2013

FDA-Approved for Any *BRAF* ^{V600E} mutant Tumor

- **Treatment with dabrafenib + trametinib**





Kato *et al., Clin Cancer Res* 2021

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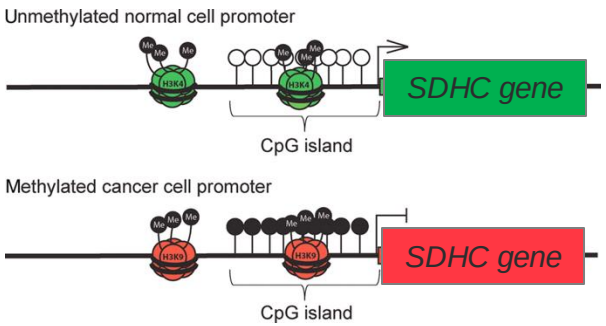

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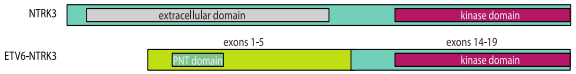

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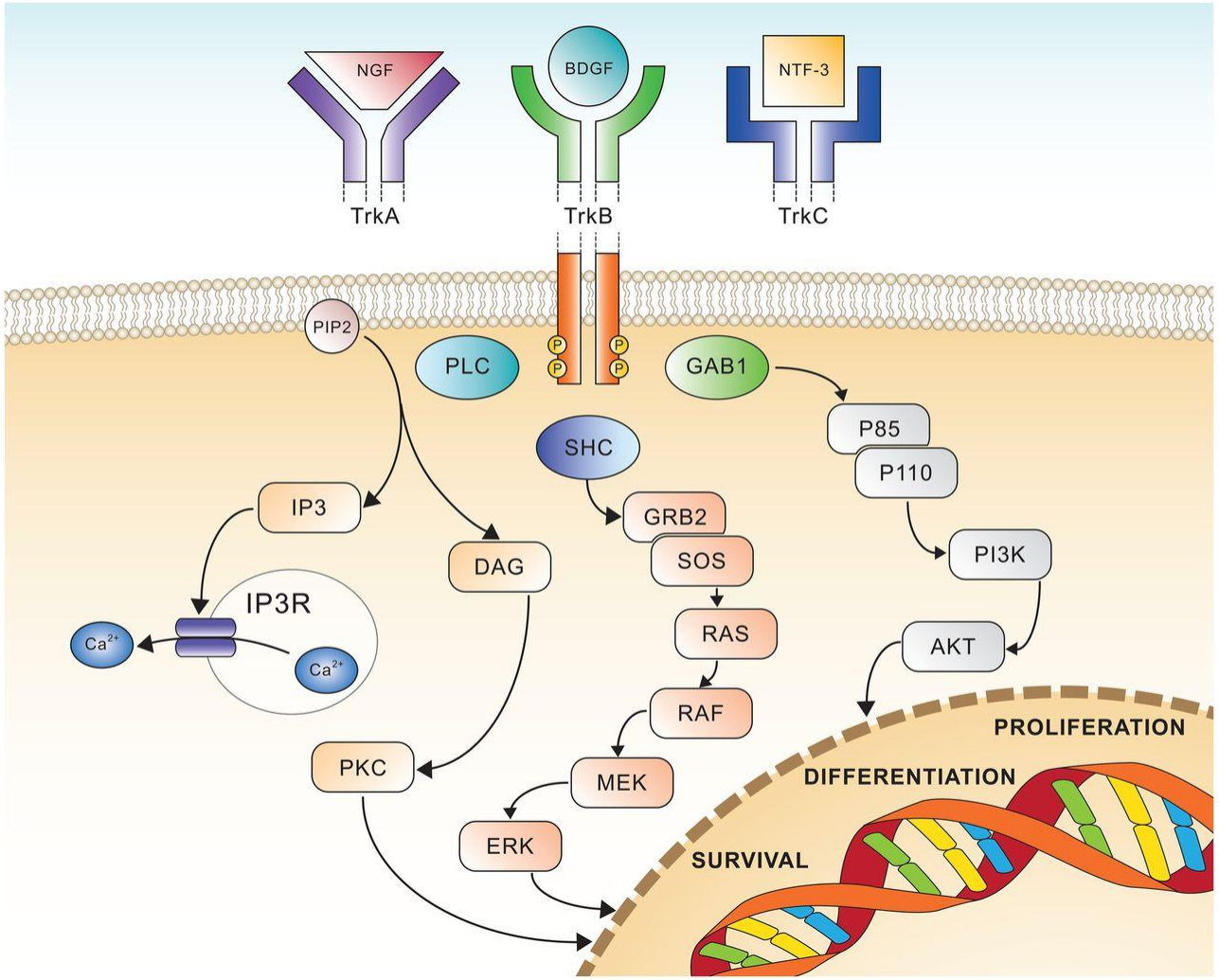
Brenca et al., J Pathol

Shi et al., *JTM*.

Neurotrophic tropomyosin receptor kinase (*NTRK*)

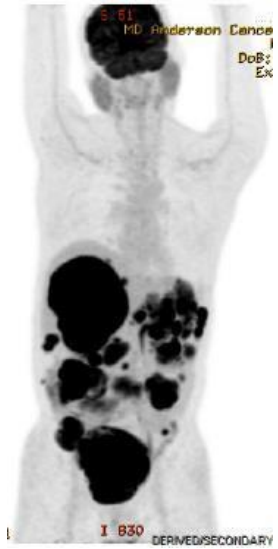


Amatu *et al.*, *ESMO Open*. 2016.

Treatment Refractory *ETV6-NTRK3* GIST

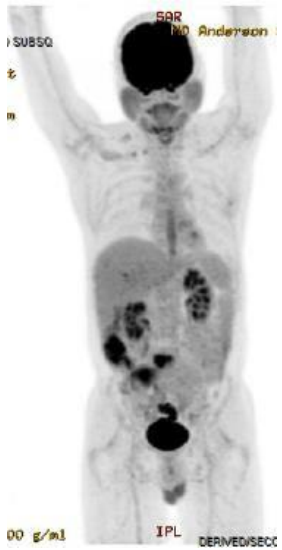
Failed 5 therapies

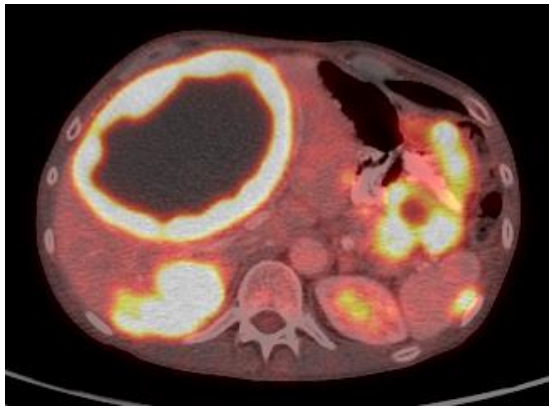
Baseline

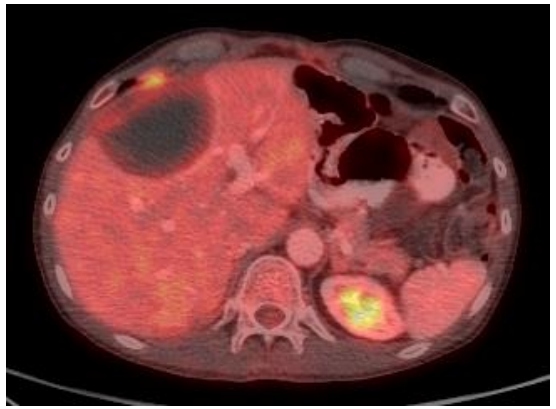


Larotrectinib

Week 8

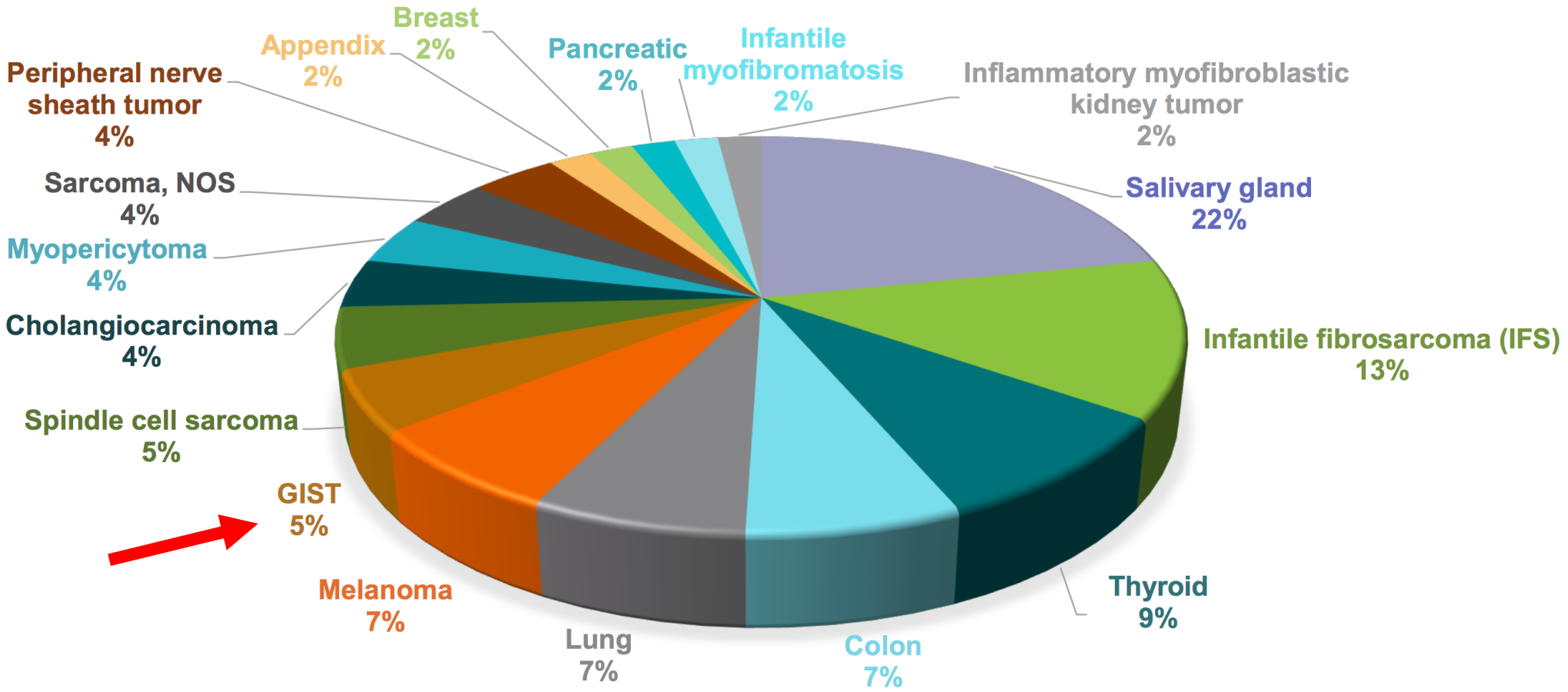






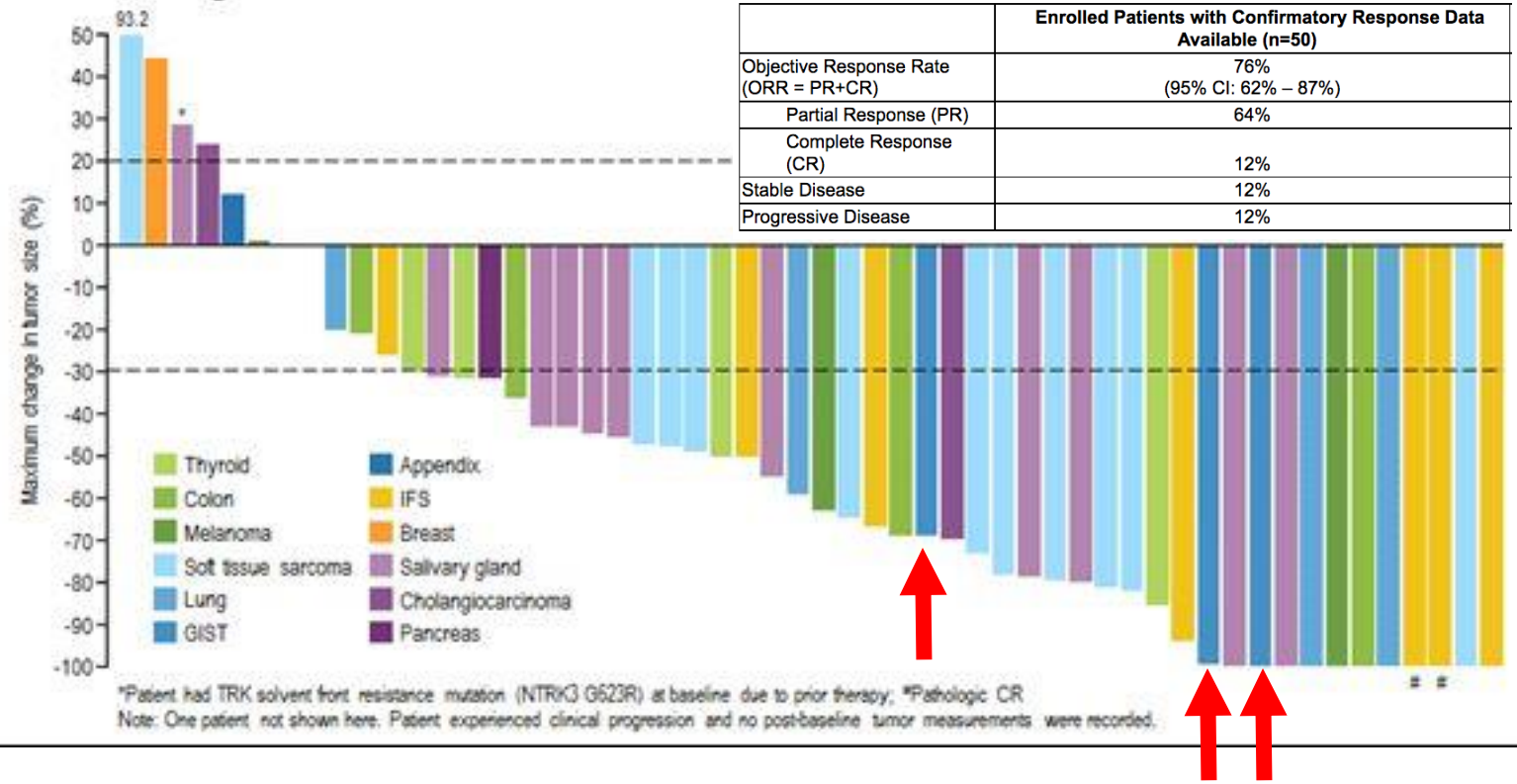
Shi et al,, *JTM* 2016.

Diversity of cancers treated - 17 unique types



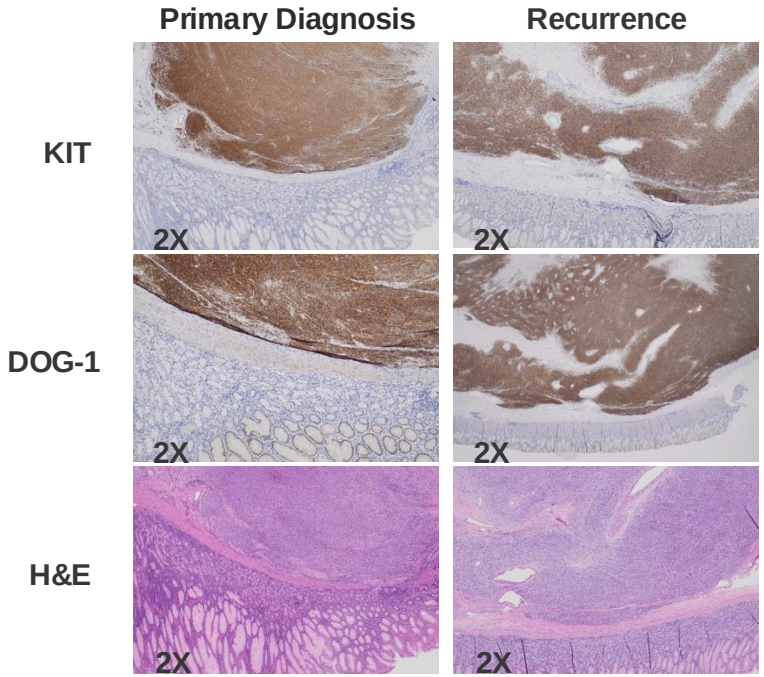
Efficacy of larotrectinib in TRK fusion cancers

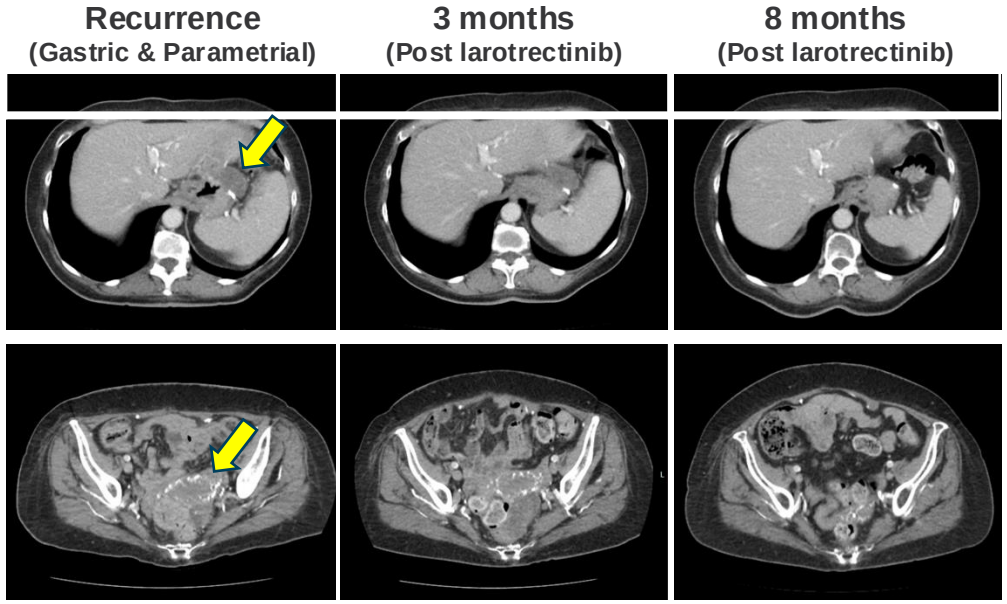
	Enrolled Patients with Confirmatory Response Data Available (n=50)
Objective Response Rate (ORR = PR+CR)	76% (95% CI: 62% – 87%)
Partial Response (PR)	64%
Complete Response (CR)	12%
Stable Disease	12%
Progressive Disease	12%

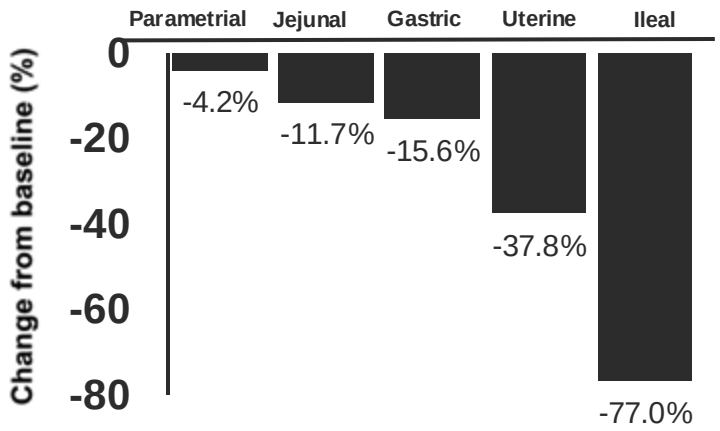


*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

Does ETV6-NTRK3 GIST Really Exist? Yes….







Tumor Location	Pathologic Size (cm)	Viable Tumor Cells
Parametrial (left)	4.5 x 3.0 x 1.8	1% *
Jejunal (mesentery)	4.5 x 4.2 x 2.3	1% *
Gastric (greater curvature)	4.3 x 2.5 x 0.6	1% *
Uterine (posterior)	1.4 x 0.2 x 0.3	1% *
Ileal (mesentery)	1.4 x 1.2 x 0.7	1% *

* Hyalinized nodule

Ranjbarian *et al., Clin Cancer Res* 2025

Does ETV6-NTRK3 GIST Really Exist? Yes….

Case	Age (y)	Sex	Location	Size (cm)	KIT (CD117)	DOG-1	*KIT* Mutation	*PDGFRA* Mutation	*NTRK* Fusion
1	67	F	Gastric	4.5	Positive	Positive	WT	WT	*ETV6-NTRK3*
2	52	F	Mesentery	10	Positive	Positive	WT	WT	*ETV6-NTRK3*
3	56	M	Gastric	16	Positive	Positive	WT	WT	*ETV6-NTRK3*
4	44	M	Rectum	5	Positive	Positive	WT	WT	*ETV6-NTRK3*
5	53	F	Pelvic	20	Positive	Positive	WT	WT	*ETV6-NTRK3*
6	34	F	Esophageal	8.4	Positive	Positive	WT	WT	*ETV6-NTRK3*

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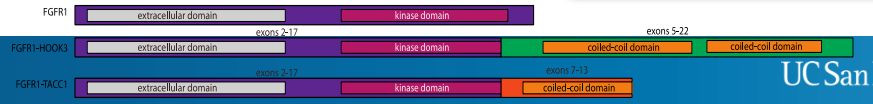
Shi et al., *JTM*.

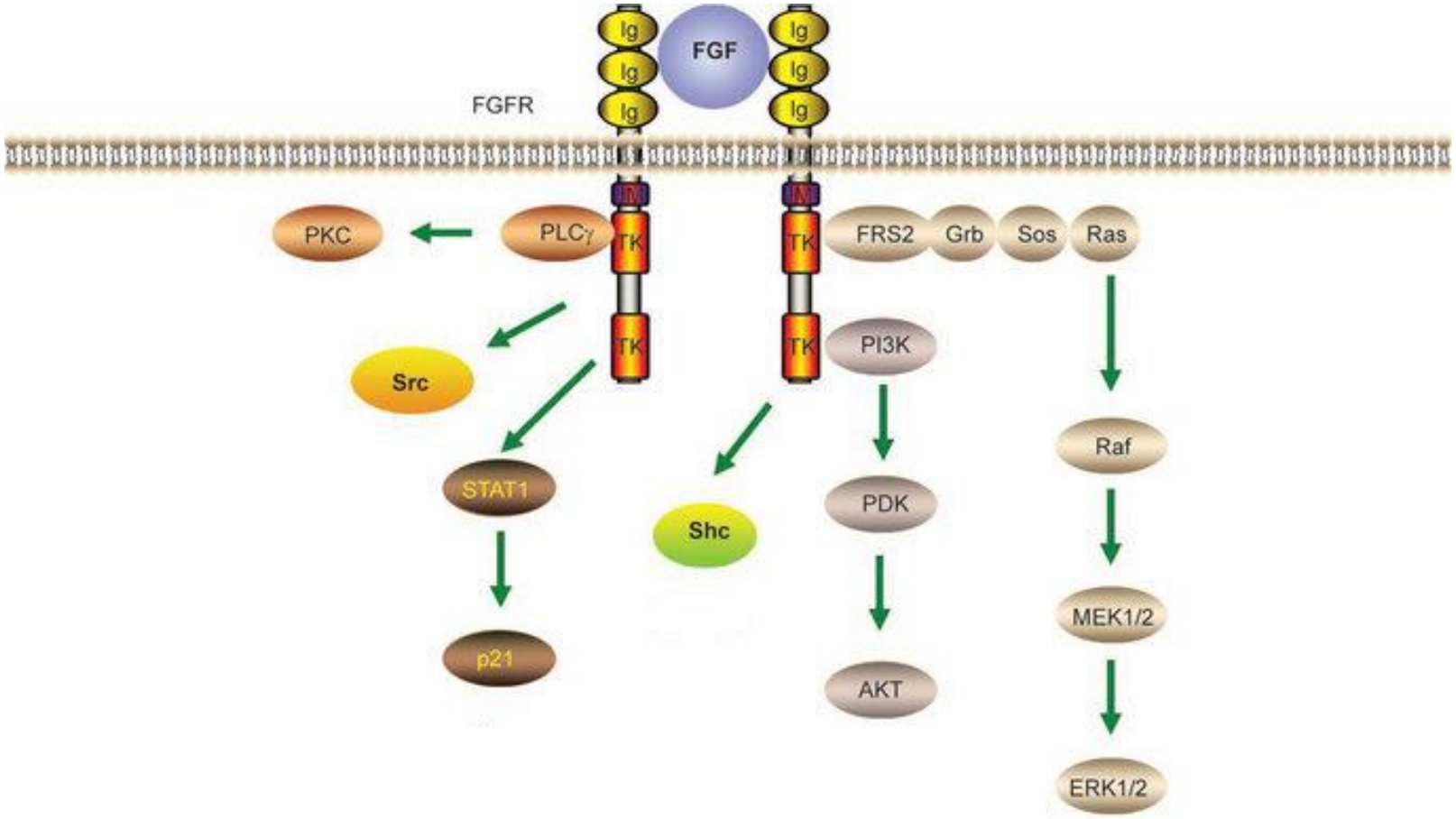
2016 — FGFR1 fusions

Quadruple WT (*KIT/PDGFRA/ RAS-P/SDH*) have FGFR1-HOOK3 & FGFR1-TACC1 fusions

Shi et al., *JTM*. 2016

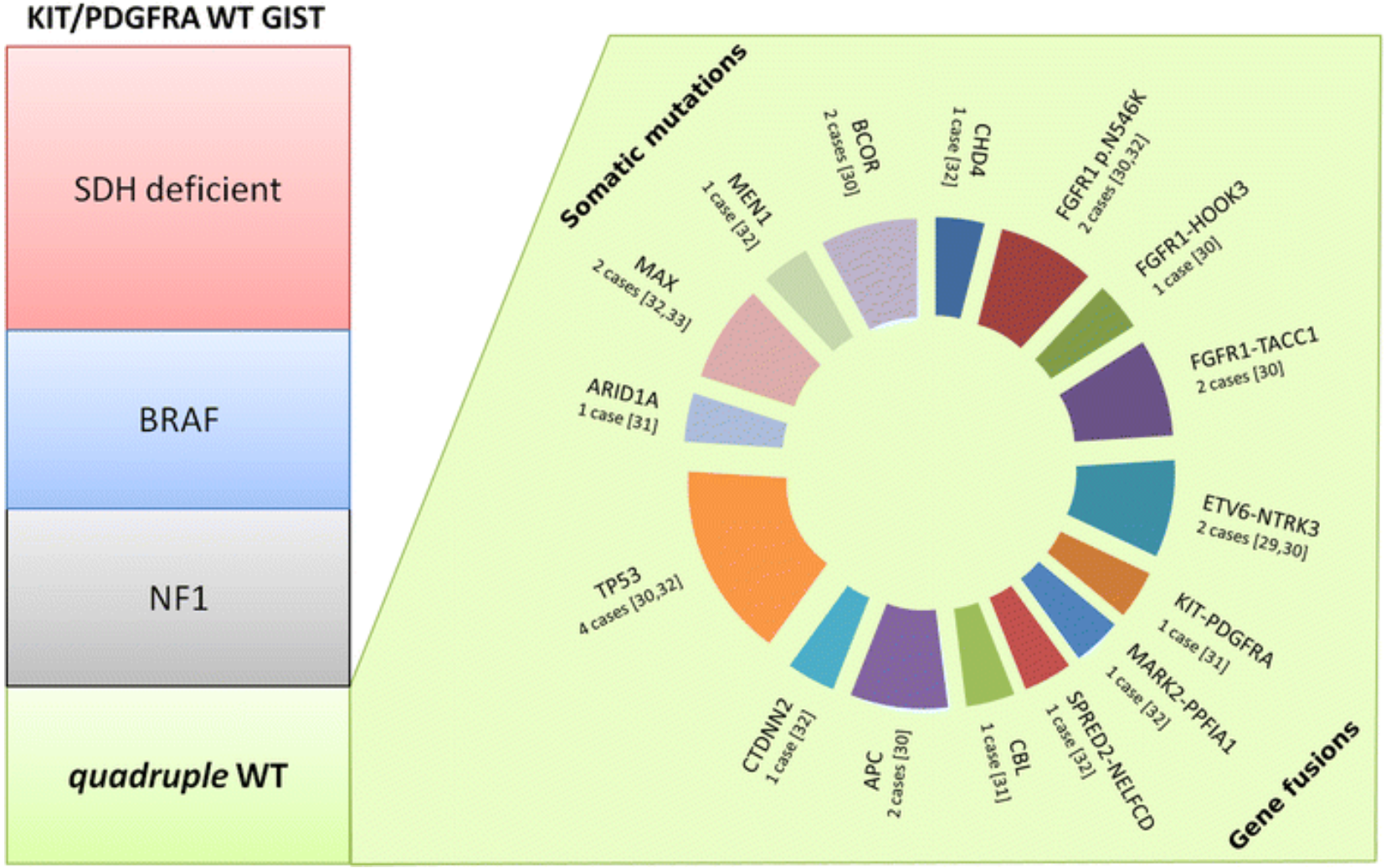


Fibroblast Growth Factor Receptor 1 (*FGFR1*)



Amatu *et al.*, *ESMO Open*. 2016

Fractionation of *KIT/PDGFRA* Wild-Type GIST



Nannini *et al.*, *JTM*. *May* 2017.

Abandoning The Term “Wild-Type” GIST

Journal of the National Comprehensive Cancer Network

The Call of “The Wild”-Type GIST: It’s Time for Domestication

Maha Alkhuziem, MBBS, MAS; Adam M. Burgoyne, MD, PhD; Paul T. Fanta, MD; Chih-Min Tang, PhD; and Jason K. Sicklick, MD

“Unclassified” GIST

Alkhuzeim et al., JNCCN. May 2017.

GIST Biology Extends Beyond *KIT* Mutations

Stomach

KIT
PDGFRA
Germline SDHx
Epimutant SDH

Small Intestine

KIT
Gene Fusions
Germline NF1

Colon

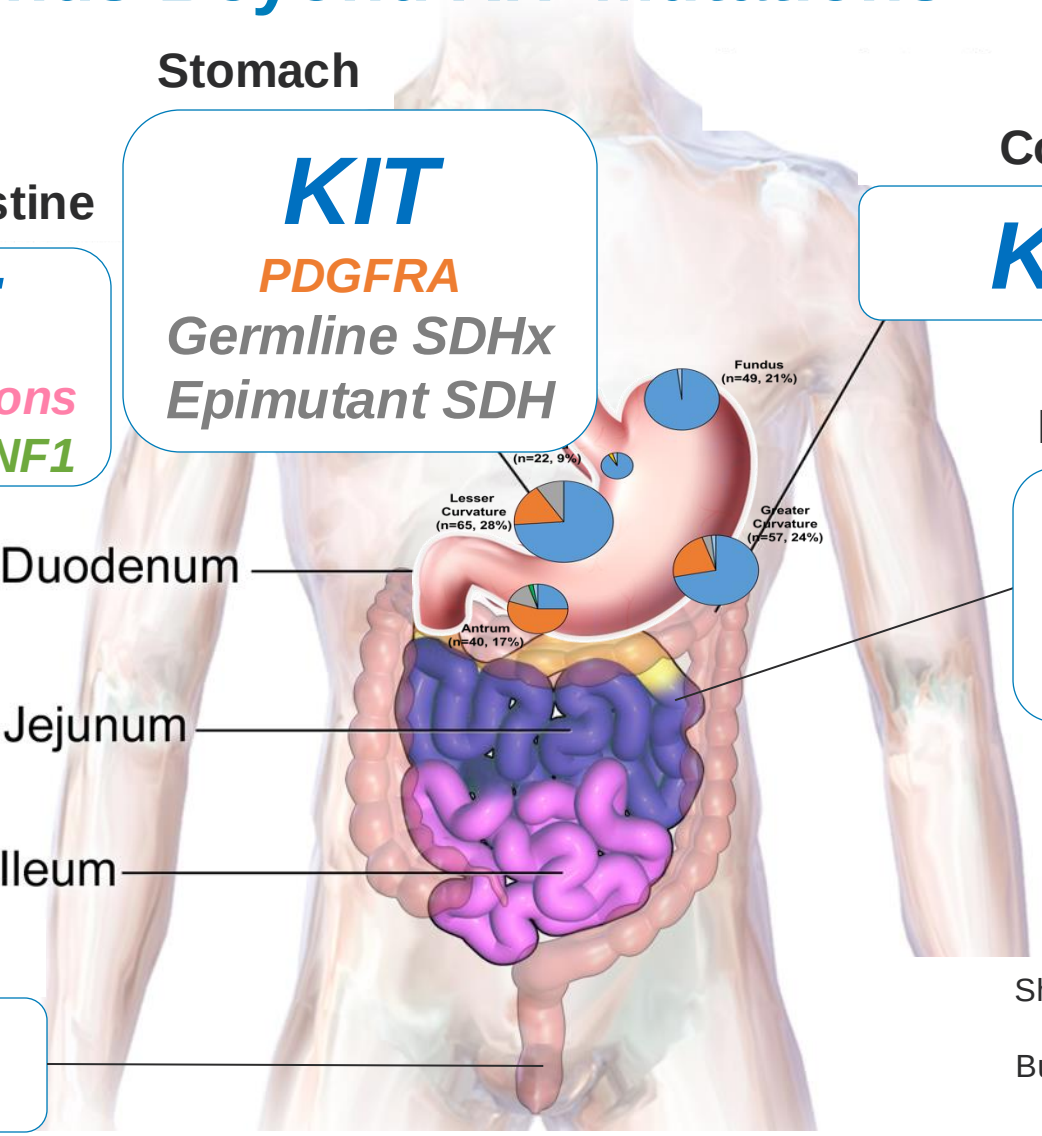
KIT

Duodenal-Jejunal Flexure

KIT
BRAF V600E
Somatic & Germline NF1

Rectum

KIT

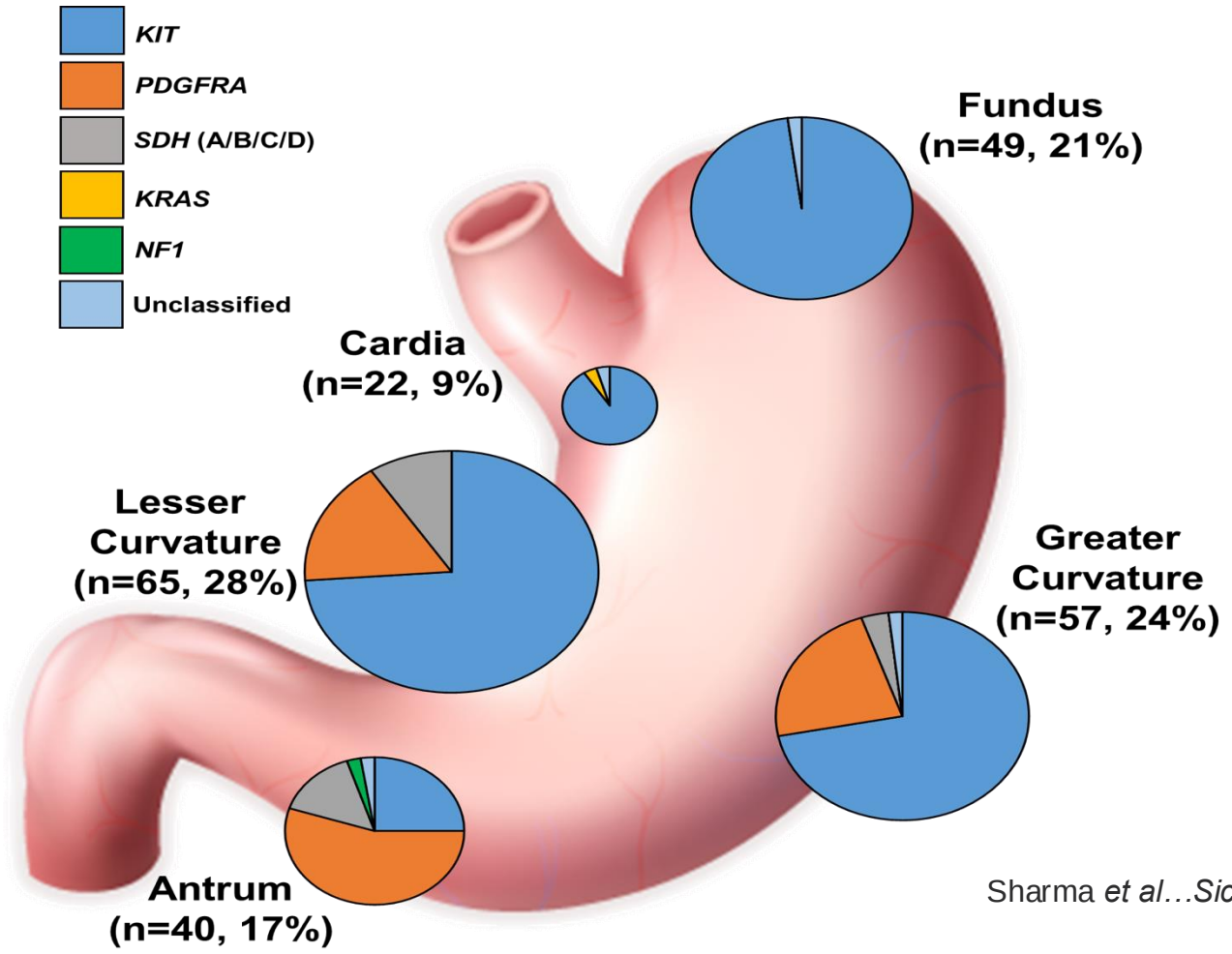


Sharma *et al…Sicklick, Clin Cancer Res*, 2022
Stuart *et al…Sicklick, JSO*, 2019
Burgoyne *et al…Sicklick, JCO Prec Onc*, 2017
Shi *et al…Sicklick, J Transl Med*, 2019

Succinate Dehydrogenase (SDH)-Deficient GIST

Stomach

Germline SDHx
Epimutant SDH



Sharma *et al…Sicklick, Clin Cancer Res*, 2022

SDH-Deficient GIST

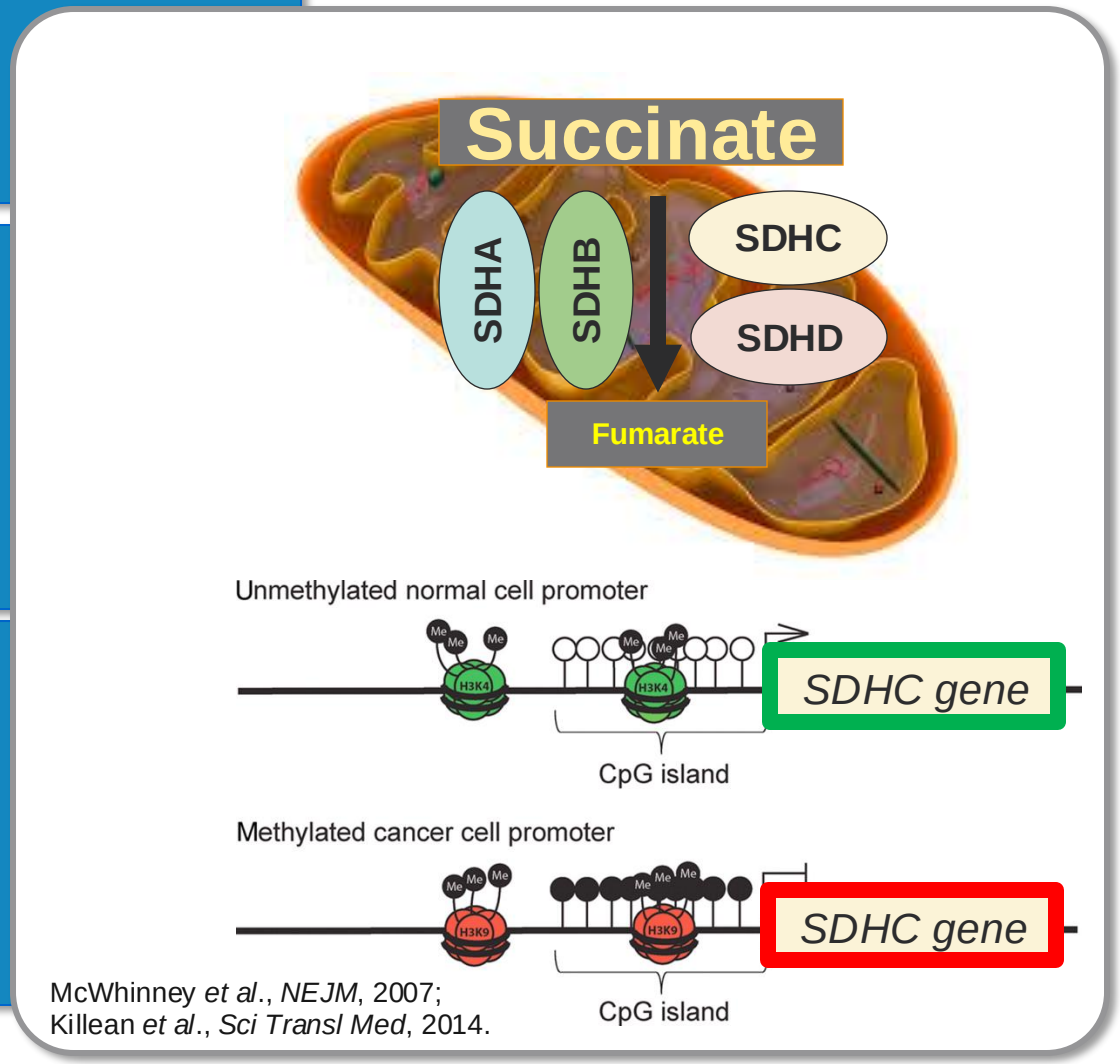
- Lack SDHB expression = “deficient”
- ~10% of all GIST (~600 cases/year)
- Blood + peritoneal + lymphatic spread

Carney-Stratakis Syndrome
(Hereditary Paraganglioma-Pheochromocytoma Syndrome)

Germline *SDHx* mutations
Hereditary
Often in adolescents & young adults
Paraganglioma (PGL)

Carney’s Triad (SDH Epimutant)

SDHC promoter hypermethylation
Sporadic
Teenage females
PGL + Pulmonary Chondroma (benign)



McWhinney *et al*., *NEJM*, 2007;
Killean *et al*., *Sci Transl Med*, 2014.

Natural History of SDH-Deficient (SDH-def) GIST

- Limited data on the natural history of SDH-def GIST comes from case reports/series.
- Often describe SDH-def GIST
  - Indolent
  - Pediatric
  - Insensitive to most TKIs
  - Recalcitrant to serial or more extensive surgical resections.
- Yet, we are seeing SDH-def GIST patients dying from this cancer with limited understanding of why their disease is more aggressive.

UC San Diego Moores Cancer Center

NIH National Cancer Institute

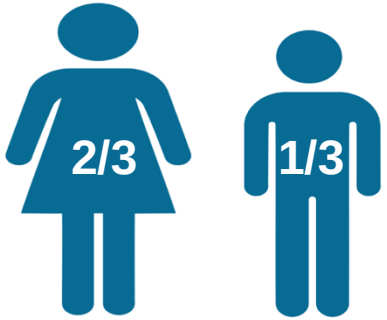
The Life Raft Group

Patient Demographics

- 256 patients across the world

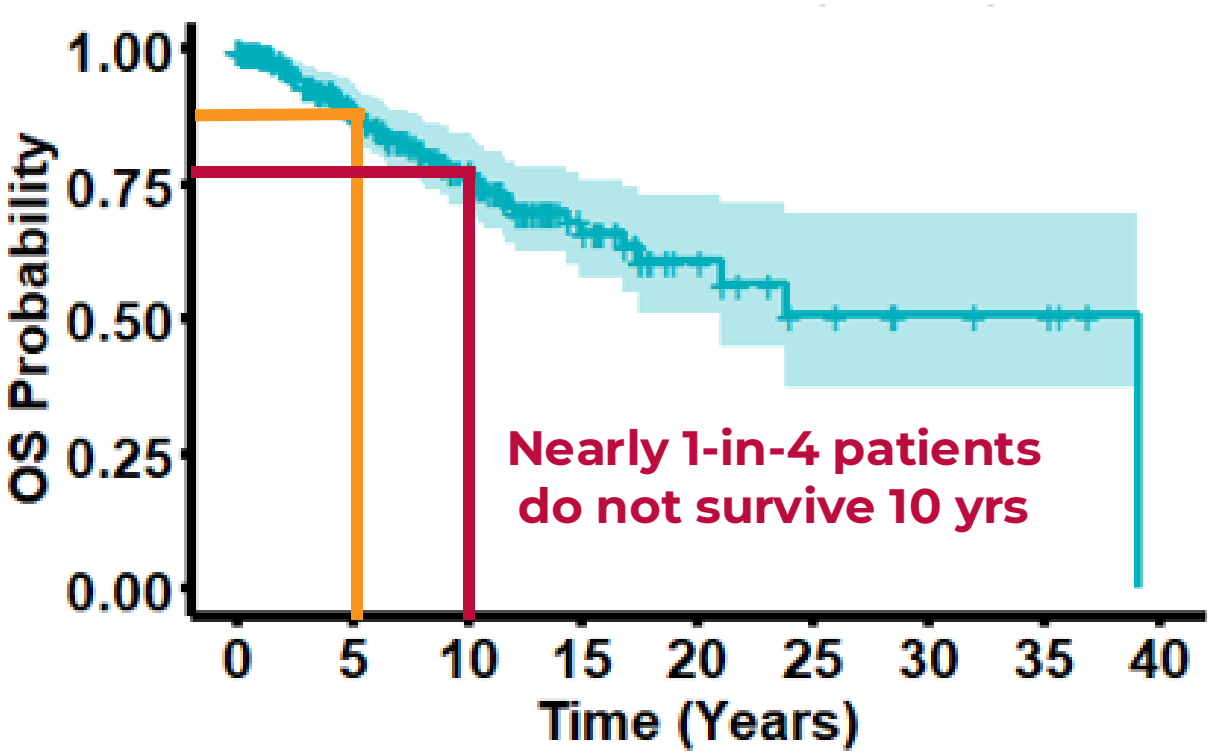
- Median age at diagnosis: 29 yo (range, 5 – 79 yo)

- Sex: 68% female, 32% male



Unpublished Data

Natural History of SDH-def GIST: Overall Survival (OS)



“Indolent disease”
Median OS 39 yrs

“Aggressive disease”
5-yr OS: 89%
10-yr OS: 77%

Unpublished Data

UC San Diego
Moores Cancer Center

NIH National Cancer Institute

The Life Raft Group

In 2020, FDA Approved Drugs (TKIs) Were Generally Ineffective

		N	CR	PR	Best ORR
FDA-approved GIST TKIs	Imatinib	61	0	2	3%
	Sunitinib	49	1	4	10%
	Regorafenib	16	0	3	19%
	Ripretinib	2	0	0	0%
SDH-def GIST studies	Linsitinib	15	0	0	0%
	Vandentinib	9	0	0	0%
	Guadecitabine	7	0	0	0%

Boikos, *JAMA Onc*, 2016.
Heinrich, *JAMA Onc*, 2017.
Janeway, *Peds Blood Can*, 2009.
Liu, *Medicine*, 2017.
Ben Ami, *Ann Onc*, 2016.
Martin-Broto, CTOS, 2021.
Bauer, *Lancet Onc*, 2021.
Von Mehren, *CCR*, 2020.
Glod, *CCR*, 2020.
Wederkind, ASCO, 2020.

Objective Response Rate (ORR)

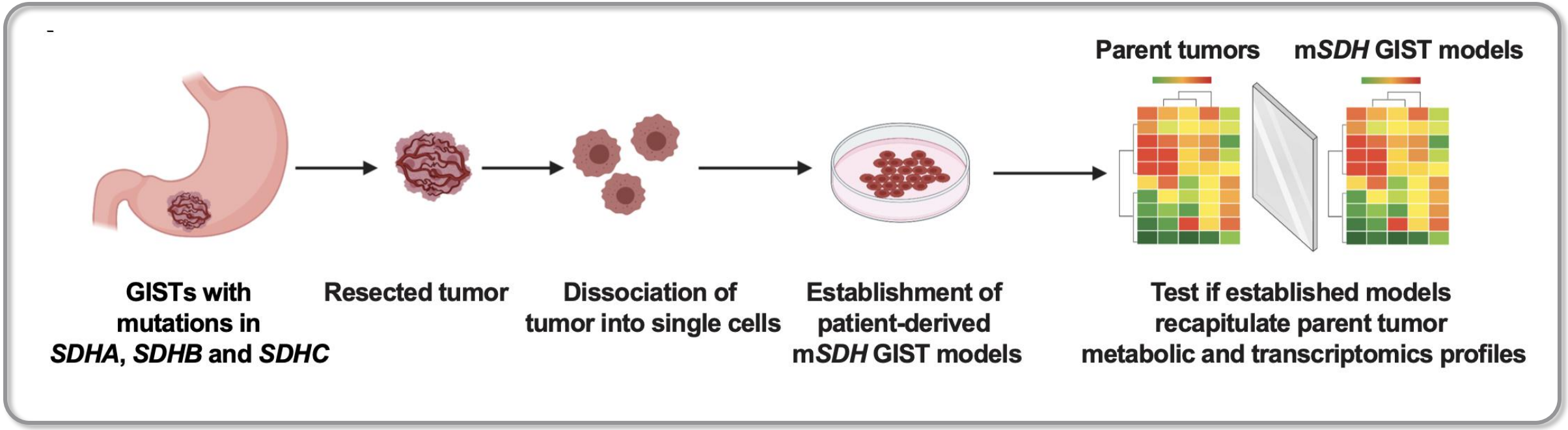
Prospective TKI Trials = 7.8% (10/129)

SDH-deficient trials = 0% (0/31)

Abbreviations: CR, complete response; PR, partial response

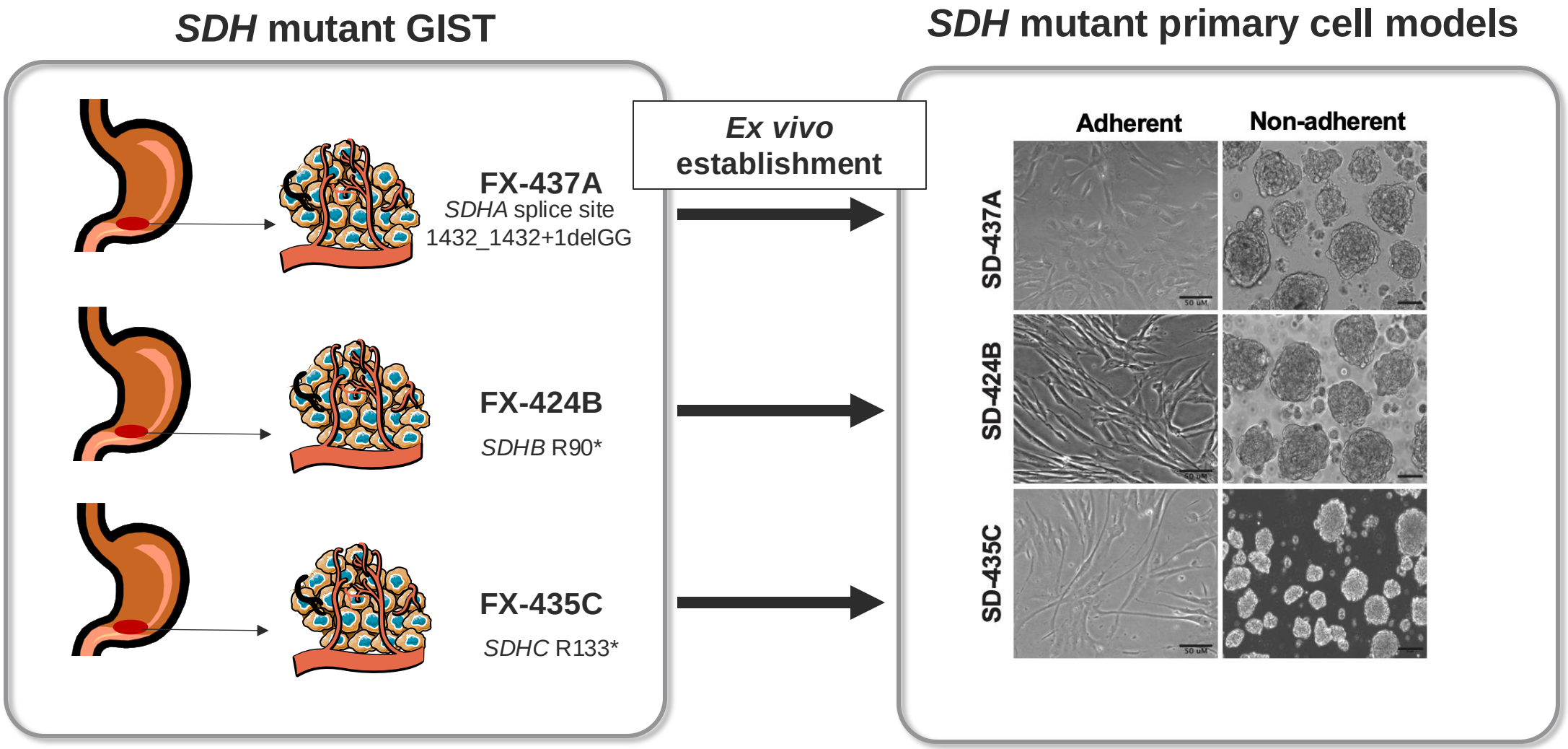
Challenge to Advancing the SDH-def GIST Field

Lack of Human-derived Preclinical Models



Yebra, Bhargava, et al…Sicklick, *Clinical Cancer Research*, 2022

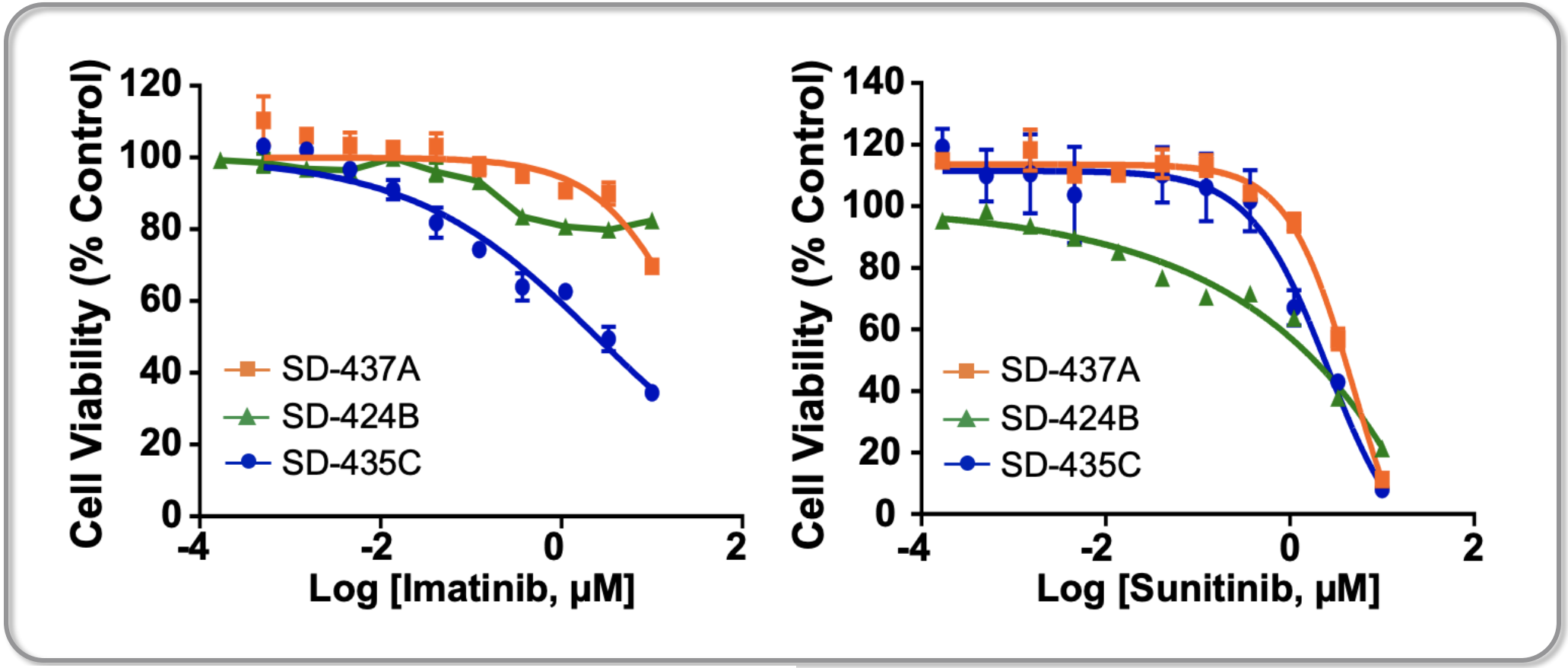
Establishment of *SDHx* Cell Models



Yebra, Bhargava, et al, *Clinical Cancer Research*, 2022.

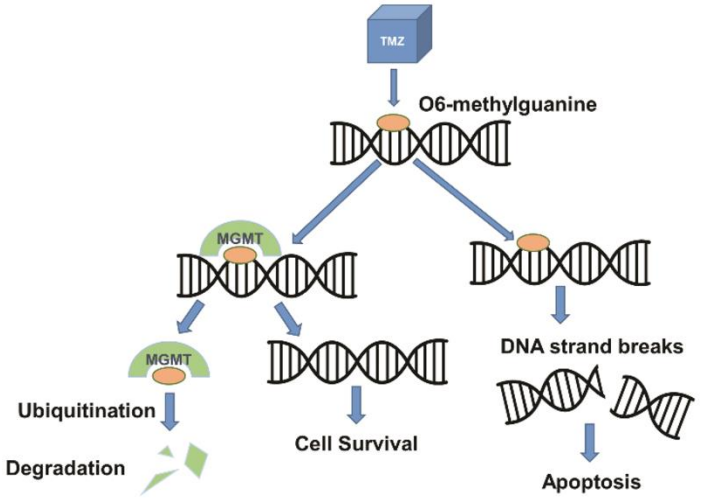
SDH-def GIST Cell Models are Imatinib/Sunitinib Insensitive

	N	CR	PR	Best ORR
Imatinib	61	0	2	3%
Sunitinib	49	1	4	10%



Yebra, Bhargava, et al…Sicklick, *Clinical Cancer Research*, 2022

Elevated Succinate Levels Inhibit DNA Damage Response (DDR)



- **Sensitizes cells to DNA Damaging agents**
  - **Temozolomide (TMZ)**

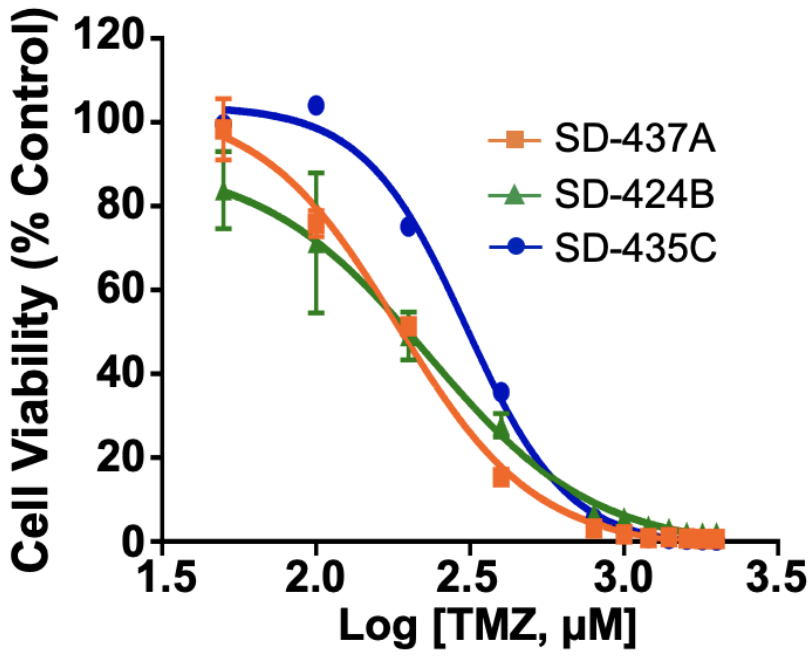
Sulkowski PL, et al, *Nat Genetics*, 2018.

- **GIST & PGL patients**

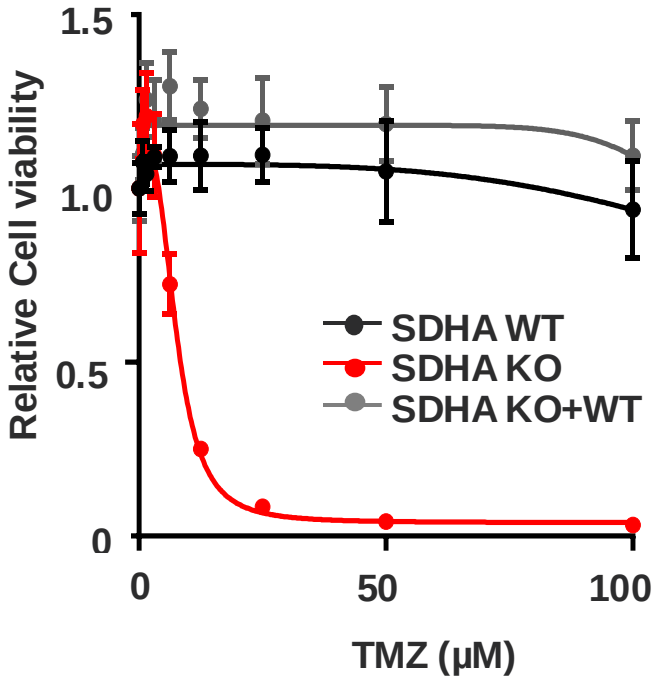
		N	CR	PR	Best ORR
GIST	Trent, 2003	18	0	0	0%
	Garcia del Muro, 2005	18	0	0	0%

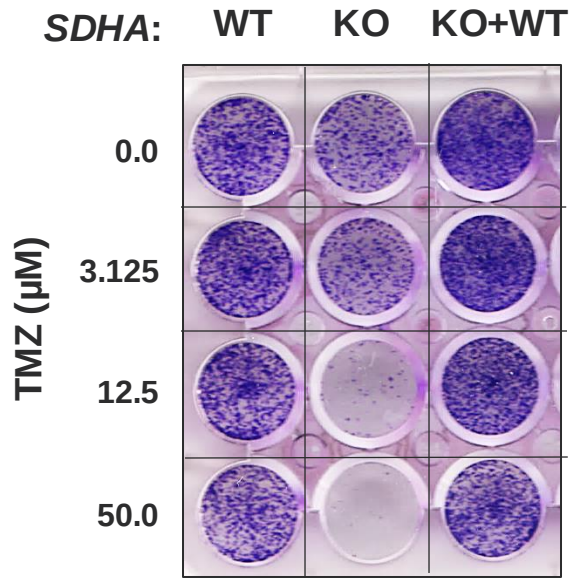
Elevated Succinate Inhibits DNA Damage Response (DDR)

Therapeutic Vulnerability to TMZ



Hap1 near-haploid line derived CML line





Michael Heinrich, MD
OHSU

Yebra, Bhargava, et al…Sicklick, *Clinical Cancer Research*, 2022

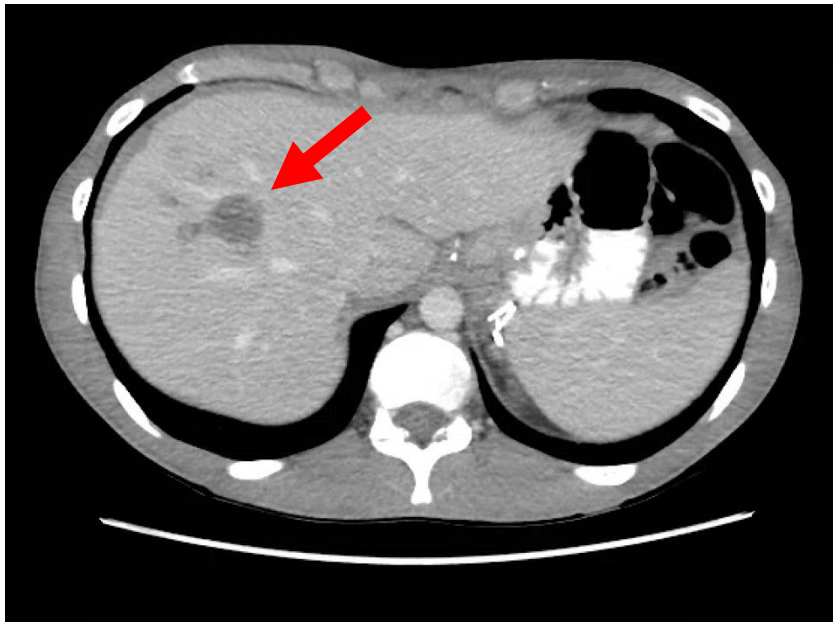
Bench-to-Bedside

Stage IV *SDHB* R90* GIST (PD on 3Ls of TKIs)

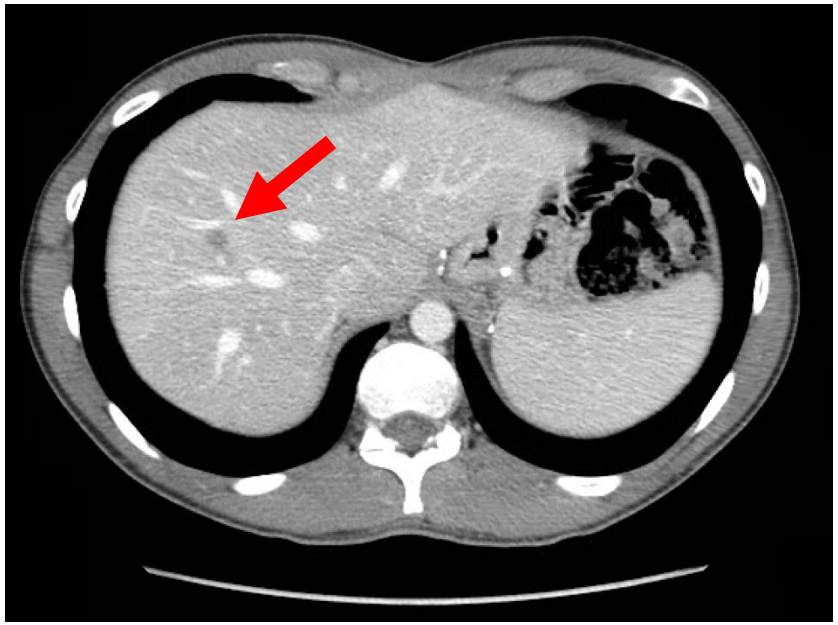
Paul Fanta, MD

START OF TREATMENT

- 22 yo male treatment with TMZ



8 MONTHS



Phase II Study of TMZ in Advanced SDH-def GIST

ClinicalTrials.gov NCT03556384

UC San Diego

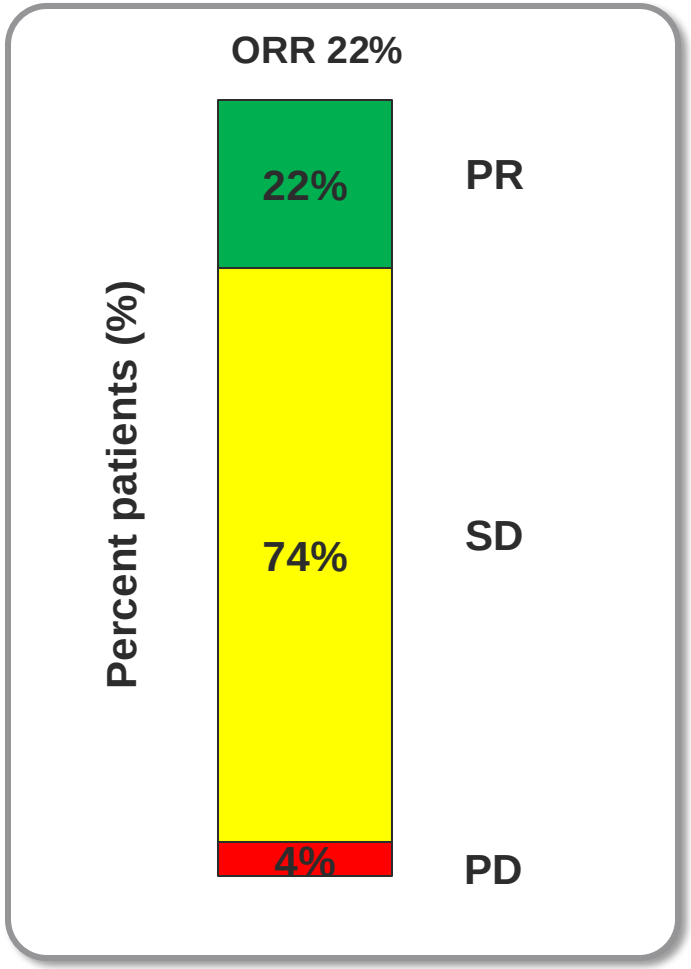
Adam Burgoyne, MD, PhD

OHSU OREGON HEALTH & SCIENCE UNIVERSITY

FOX CHASE CANCER CENTER
TEMPLE HEALTH

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

Best Overall Response Rate (ORR)



		N	CR	PR	Best ORR
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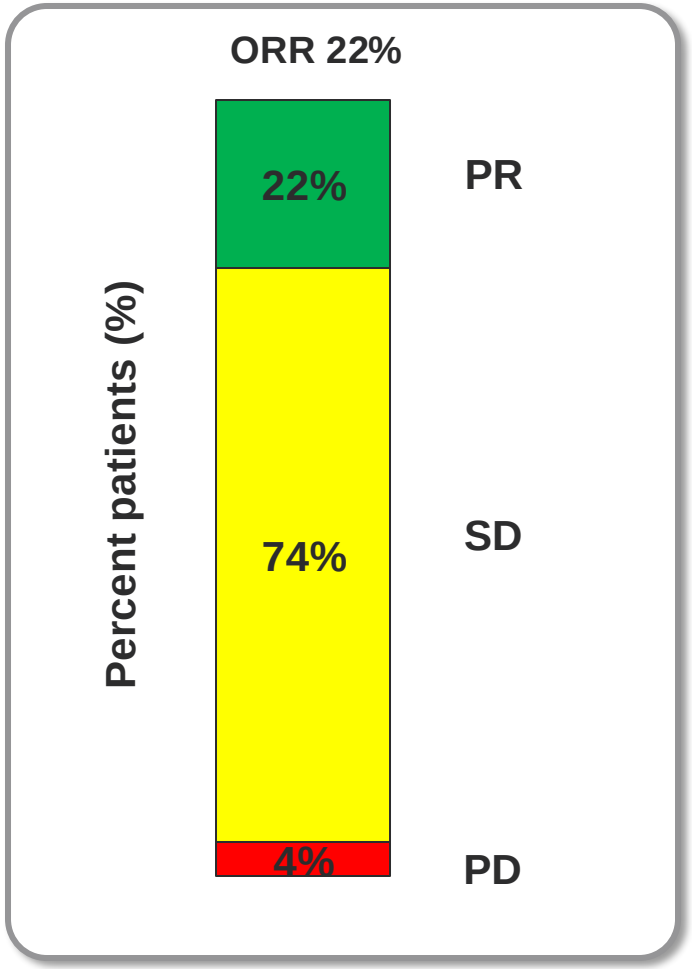
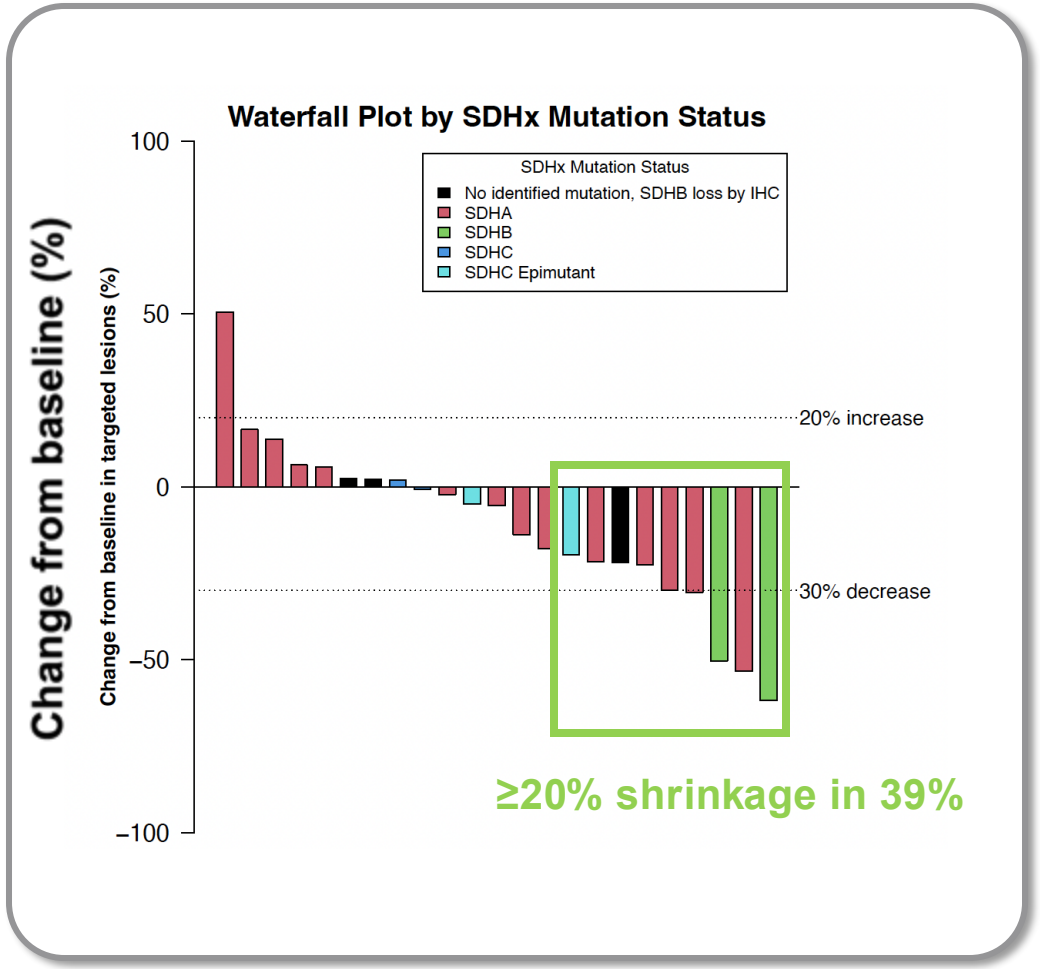
Best Overall Response Rate (ORR)



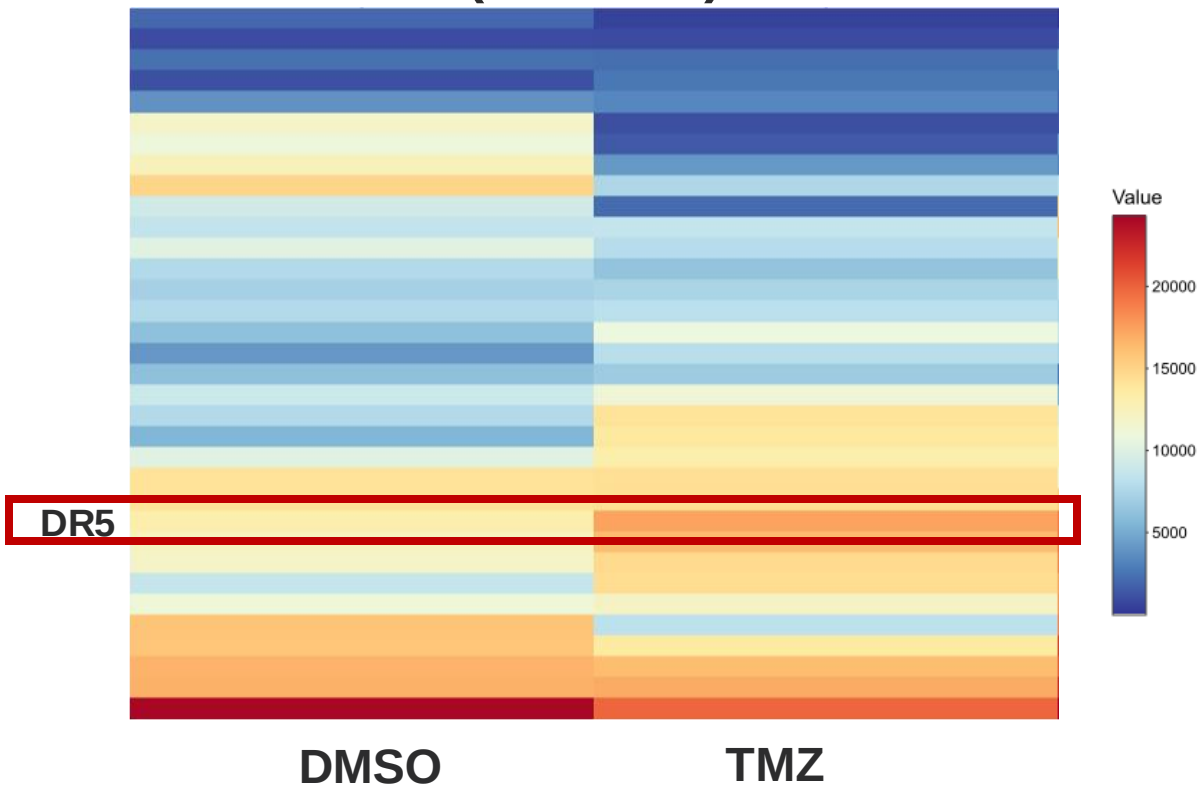


Summary

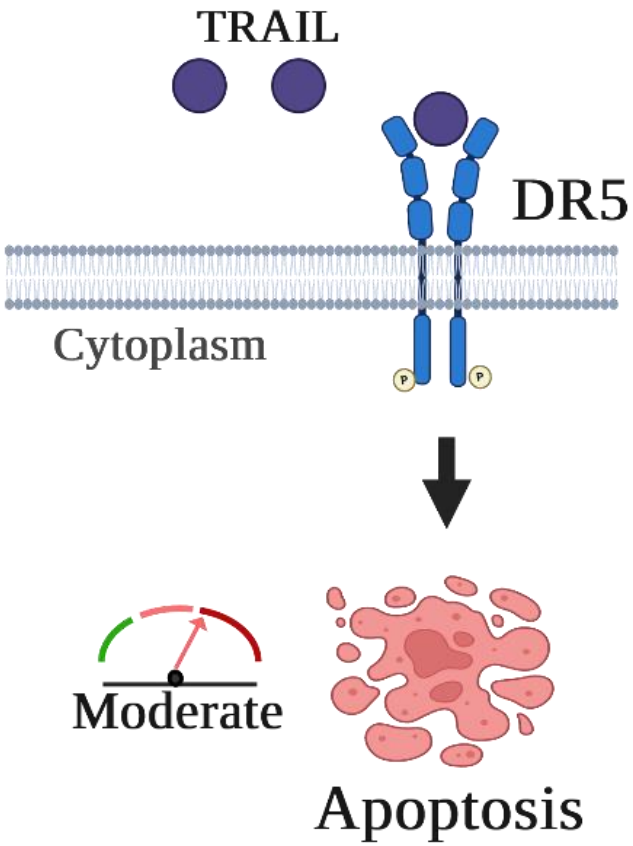
1. At the time, this multicenter study was the largest clinical trial conducted to date in SDH-deficient GIST patients.
2. TMZ had an acceptable safety profile in this population.
3. The efficacy signal with TMZ is better than that seen in prior clinical trials in the SDH-def GIST.
4. With a promising **disease control rate, TMZ enabled complete surgical cytoreduction in 5 patients (21.7%).**
5. Given the lack of efficacious therapy for treating SDH-deficient GIST, TMZ may provide a new therapeutic option and fulfill an unmet clinical need for these patients.

Temozolomide (TMZ) Increases Expression of Death Receptor 5 (DR5)

Proteome Profiler Human Apoptosis Array (SD-437A)

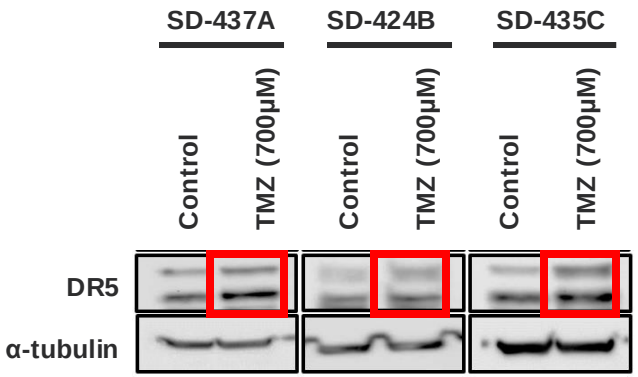


Tumor necrosis factor-Related Apoptosis-Inducing Ligand

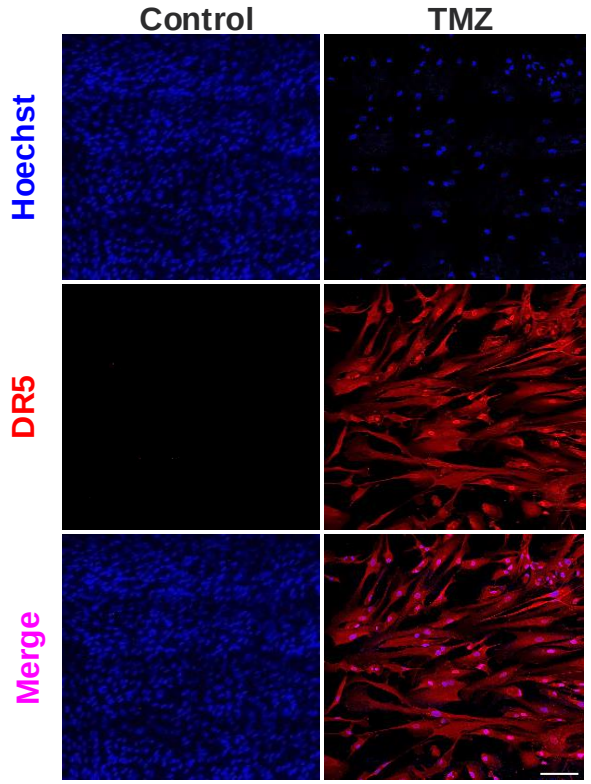


DR5 (Death Receptor 5) Levels are Enhanced upon TMZ Treatment

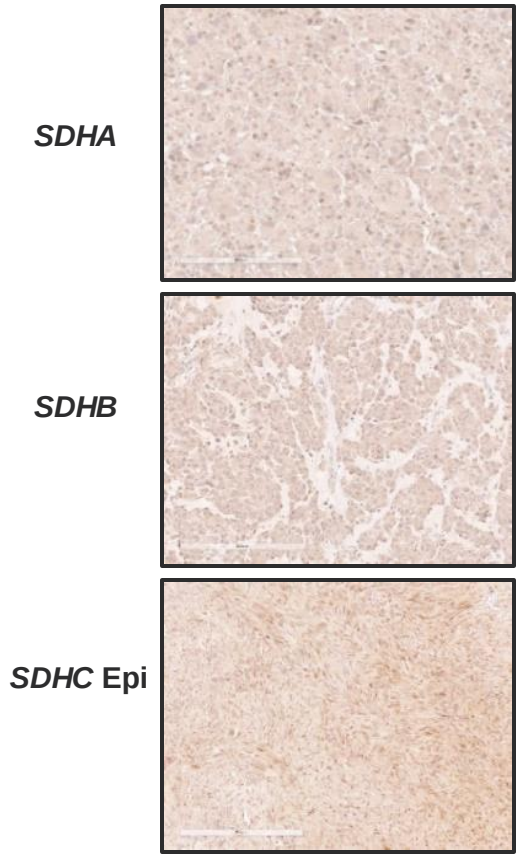
Immunoblot
(Cell Models)



Immunocytochemistry
(SD-437A)



Immunohistochemistry*
(Human GIST)



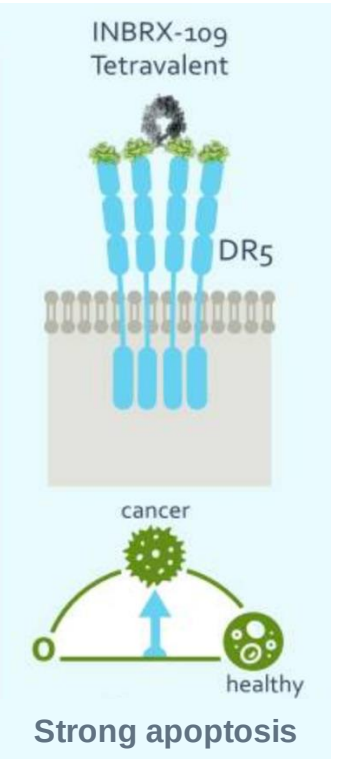
***NCT03556384**

Burgoyne *et al*, *CTOS* 2023

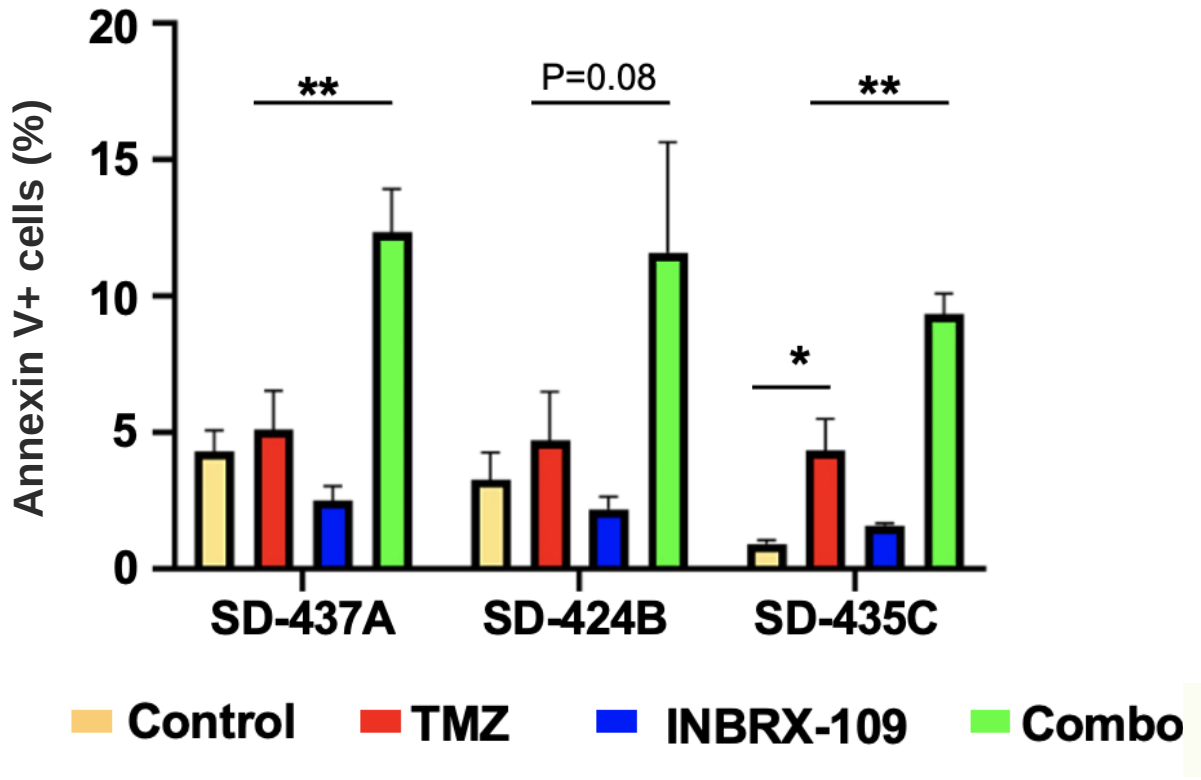
DR5 as a Therapeutic Target

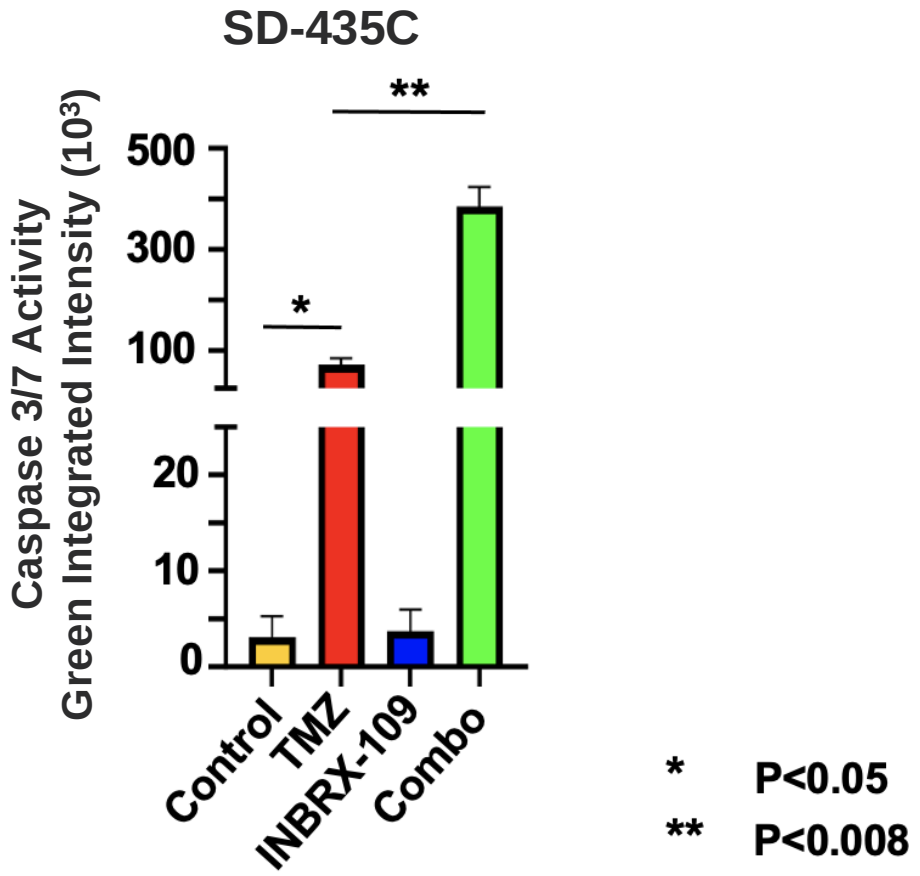
- To date, several DR5 agonists have failed in clinical trials due to unfavorable pharmacokinetics and/or inefficient bivalent/trivalent DR5 receptor clustering leading to poor agonist activity.
- Inhibrx, Inc. (located 3.2 miles from our lab in La Jolla, CA) has developed INBRX-109, a tetravalent DR5 agonistic antibody which effectively induces tumor cell death by DR5 activation.
  - INBRX-109 is ≈50–100× more potent than native TRAIL at inducing apoptosis
  - INBRX-109 is currently in clinical trials for several cancers

INHIBRX

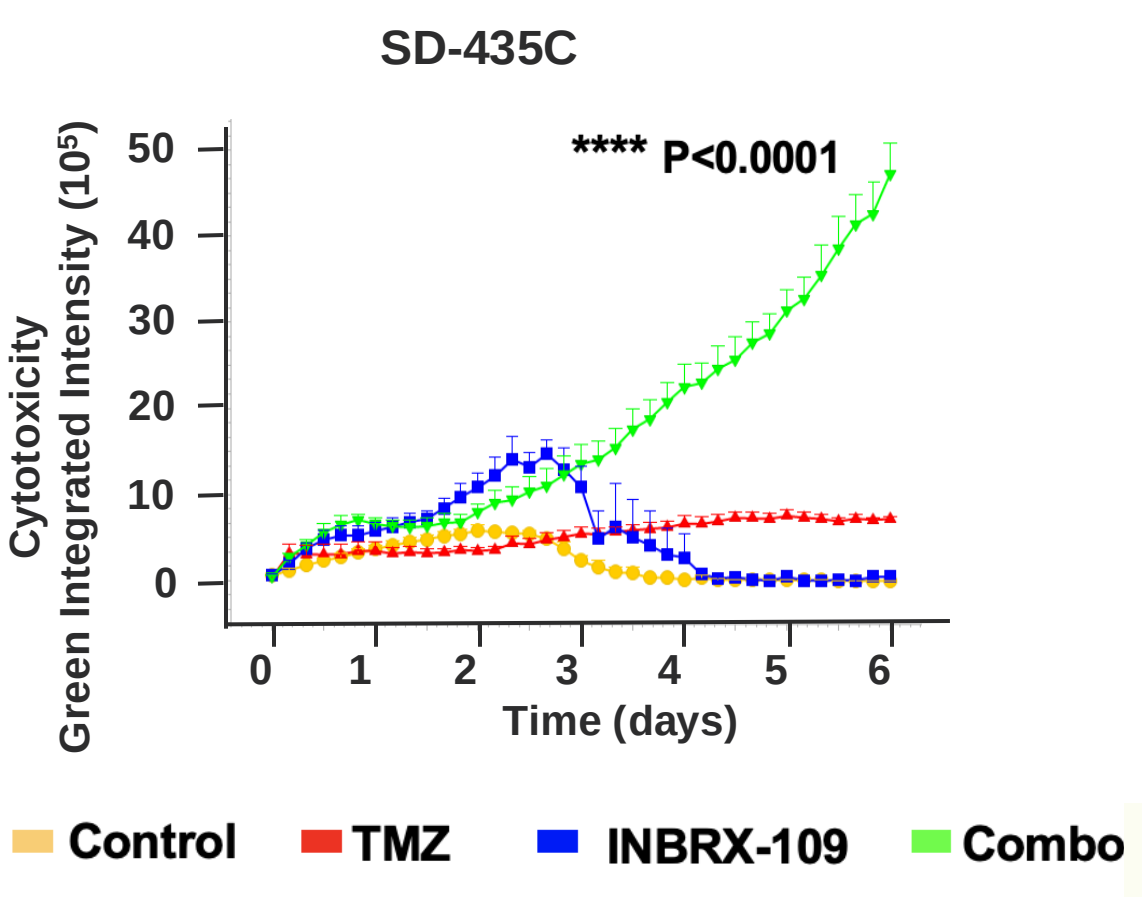


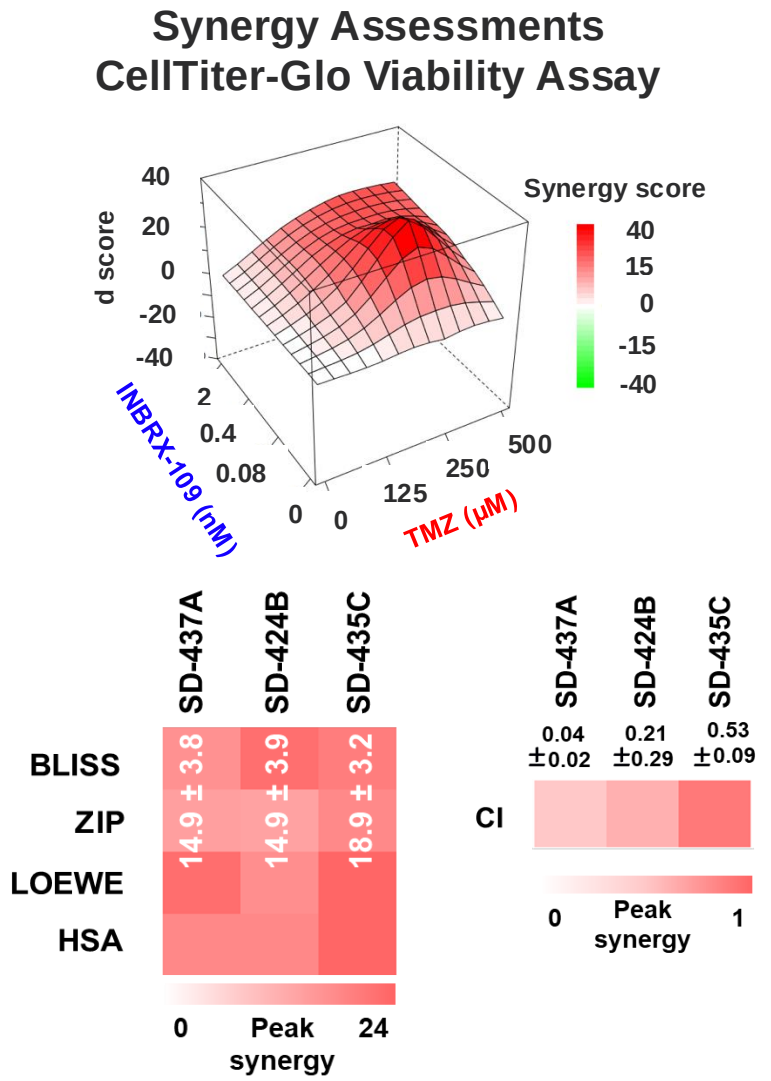
TMZ + INBRX-109 Significantly Increases Apoptosis vs. TMZ or INBRX-109 alone



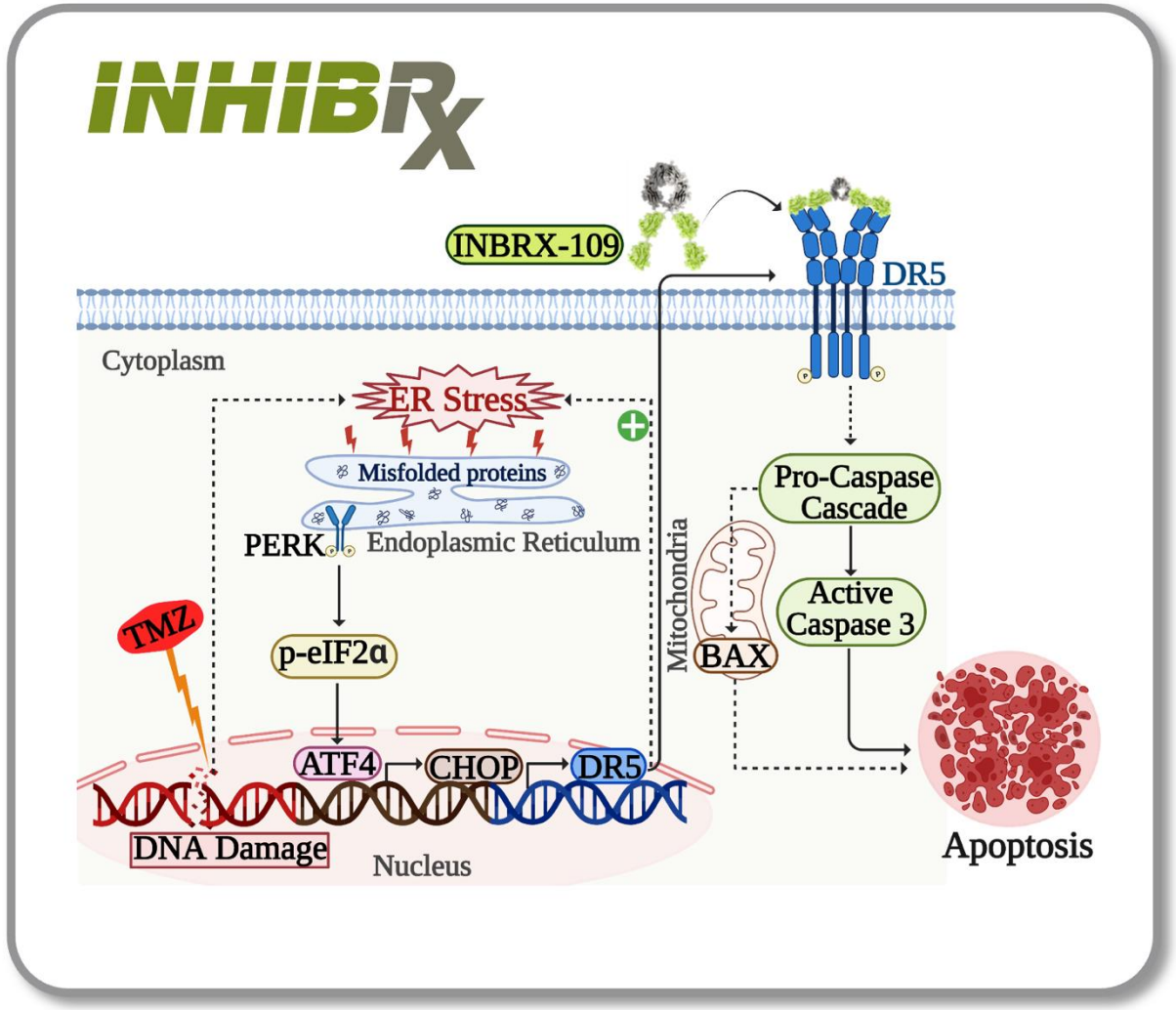


TMZ + INBRX-109 Synergistically Increases Cytotoxicity and Decreases Cell Viability





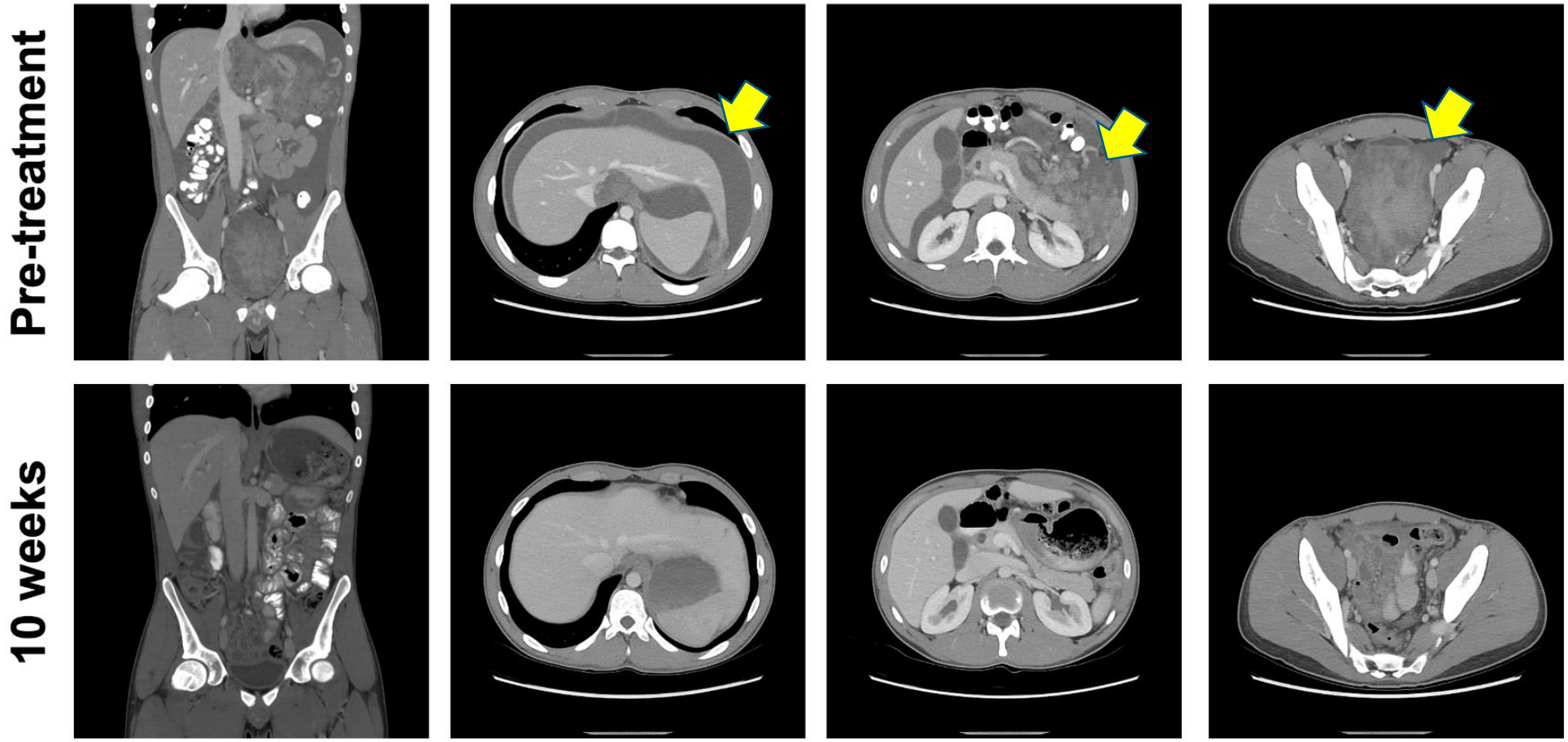
Translation: Bench-to-Bedside



Phase I Study of TMZ + INBRX-109 in SDH-Deficient Cancers (NCT03715933)

Partial Response (48% Reduction by RECIST) in *SDHB* mutant at 10 weeks

Compliments of Neeta Somaiah and David Hong, MD Anderson Cancer Center



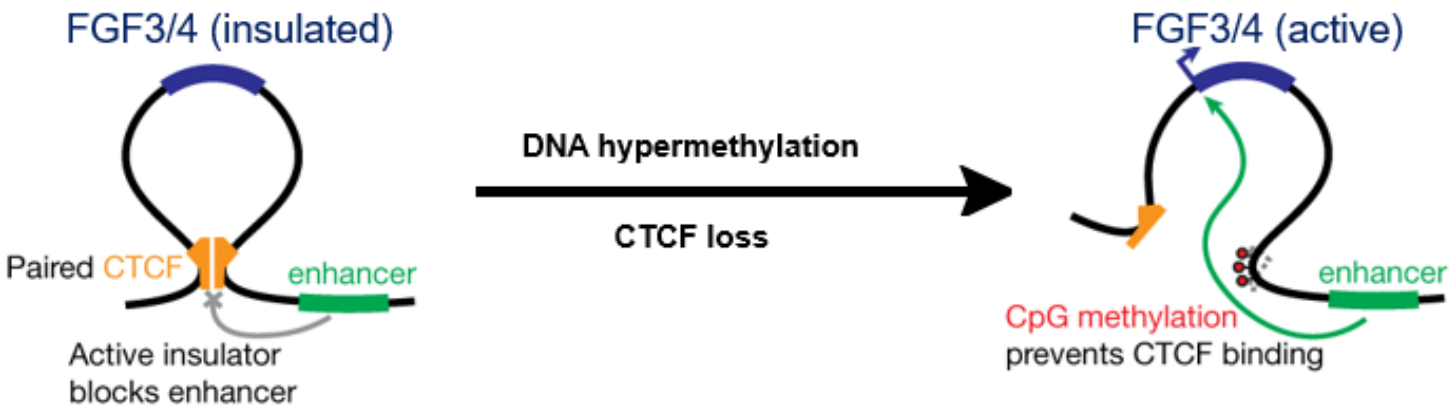
U01 Cooperative Group of 10 Institutions *SDH-Deficient GIST Translational Research and Clinical Trial Consortium*

Unite SDH-def GIST clinicians, researchers, patient advocates and industry

- Conduct clinical trials
- Develop new models for predicting drug responses in individual patients
  - **Can we start to personalize therapy? *SDH A* vs. *B* vs. *C* vs. *D*?**
- Better understand disease biology for **personalized prognostication**?

NIH/NCI MPI (John Glod)

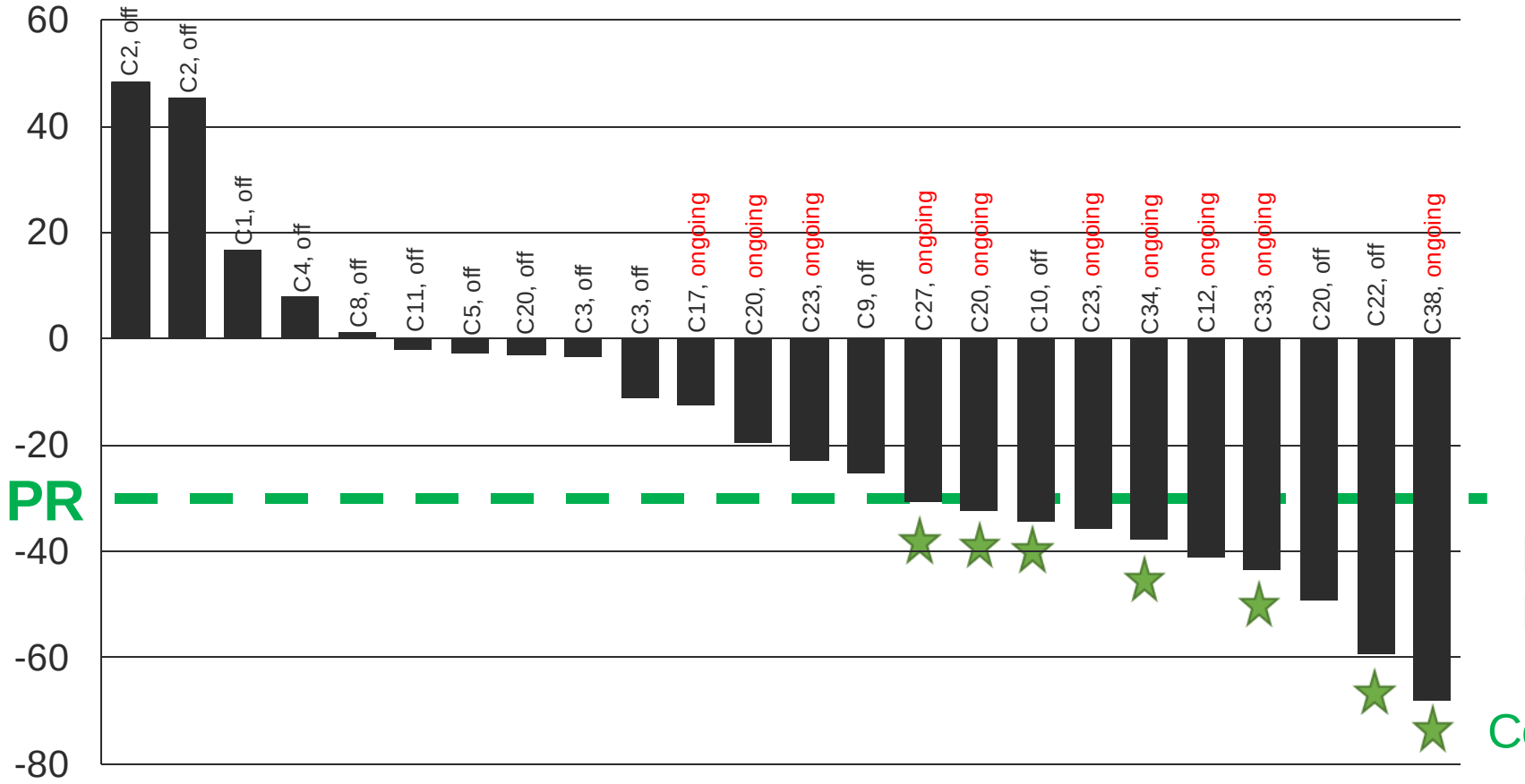
New Target Identified in 2019



- SDH-deficiency leads to DNA hypermethylation and chromatin topology changes, causing upregulation of fibroblast growth factor (FGF) ligands, *FGF3* and *FGF4* gene expression
- Dysregulation of signaling through FGFR may be oncogenic in certain cellular contexts

Flavahan *et al* Nature 2019
Slides complements of S. George

Phase 2 Study OF Rogaratinib (BAY 1163877) in Soft Tissue Sarcomas: SDH-Deficient Gastrointestinal Stromal Tumors



PR in 10/24 pts
Best ORR 41.7 %

★ Confirmed PR

Study Chair: Suzanne George, MD
Lead investigator: Priscilla Merriam, MD

Dana-Farber Cancer Institute

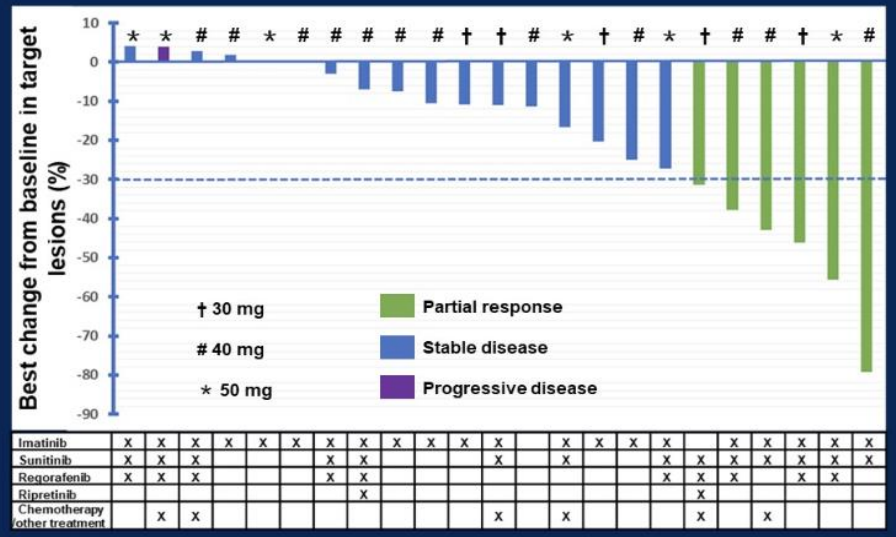
Summary

1. FGFR1-4 inhibition with rogaratinib showed promising activity with durable effect in SDH-def GIST
2. Toxicities were as expected from prior experience with rogaratinib and other agents with FGFR inhibition, and were mostly mild to moderate
3. This work demonstrates the impact of epigenetic alterations on tumorigenesis and supports the approach of targeting aberrantly activated FGFR signaling that can occur in the absence of canonical kinase mutations
4. Successful accrual of this trial in just over 2 years demonstrates the feasibility of conducting multicenter trials for SDH-def GIST patients
5. Bayer has elected to not pursue further development of this drug
6. An academic consortium lead by Dr. Suzanne George is planning a new phase 2 study of an already approved FGFR inhibitor (pemigatinib)

Olverembatinib in SDH-deficient GIST (China)

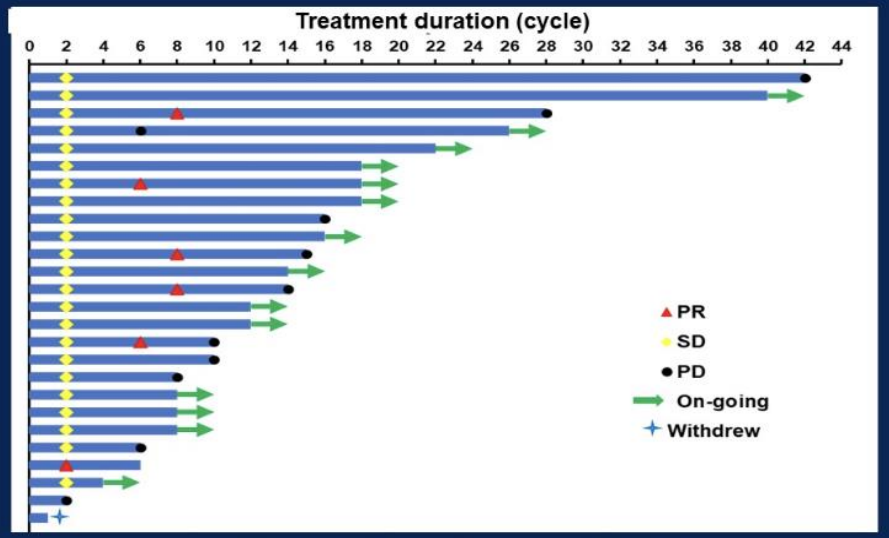
- Olverembatinib (HQP1351) is a novel TKI that targets multiple kinases such as BCR-ABL1, KIT, SRC, FGFR, and PDGFRA. The drug was approved for treatment of chronic myeloid leukemia (CML) in China.[1]

Results: Efficacy



Overall response rate, 23.1%

Among 26 evaluable patients, 6 experienced partial response (PR) as the best response despite multiple lines of prior treatment.



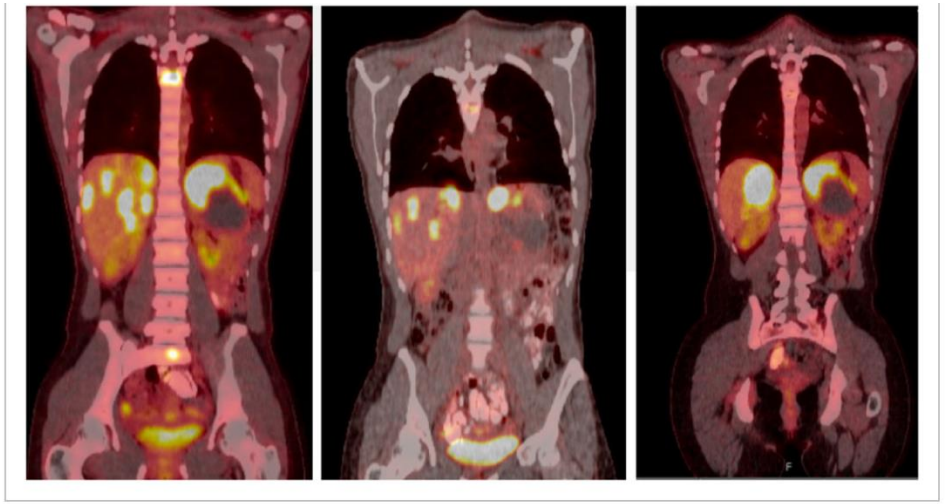
Clinical benefit rate, 92.3%

The median (range) treatment duration was 15.6 (1.8-42.3) months. A total of 24 patients had PR or stable disease (SD) > 16 weeks (4 cycles).

Anecdotal Responses

Temozolomide + Olaparib

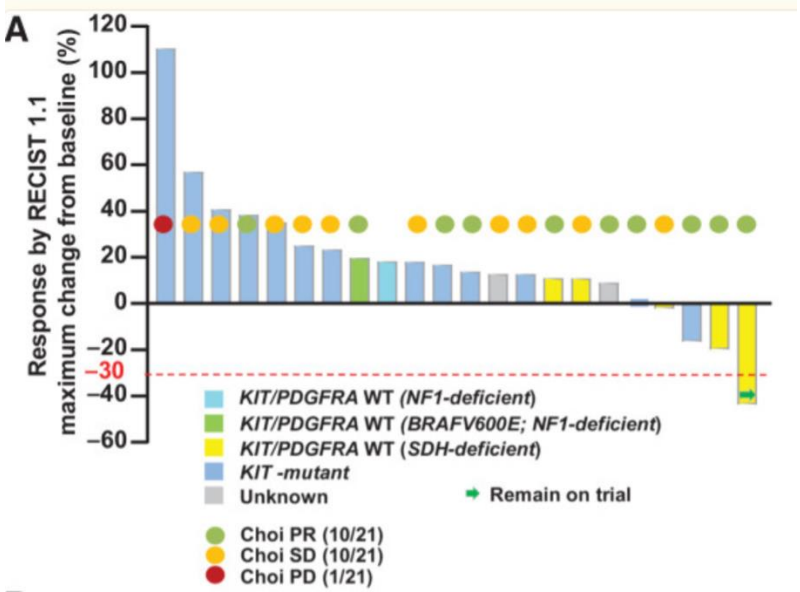
Singh …. Pashankar, Ped Blood & Cancer 2022



Imatinib + Binimetinib

1/5 patients PR

Chi et al., Clin Can Res 2022



Making Progress

		N	CR	PR	Best ORR
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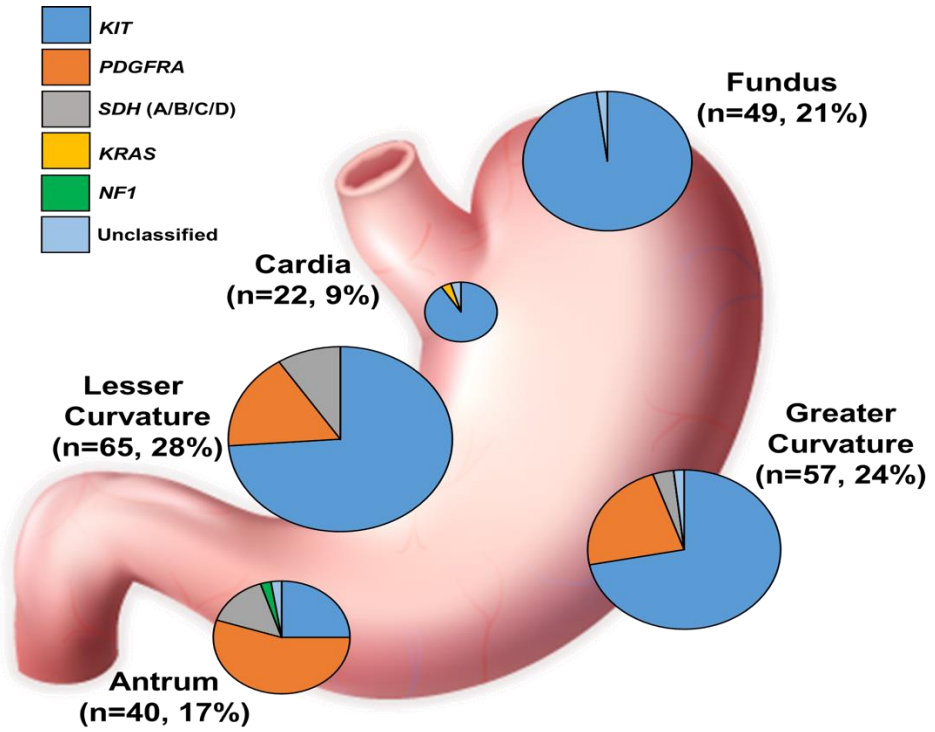
	Regorafenib	16	0	3	19%
	Ripretinib	2	0	0	0%
SDH-def GIST studies	Linsitinib	15	0	0	0%
	Vandentinib	9	0	0	0%
	Guadecitabine	7	0	0	0%
	Imatinib + Binimetinib	5	0	1	20%
	Temozolomide	23	0	5	22%
	Olverembatinib	26	0	6	23%
	Rogaratinib	24	0	10	42%

Localized Disease – No Data

Wedge resection vs. Partial Gastrectomy

Selective vs. Routine Lymphadenectomy

~~Total gastrectomy~~



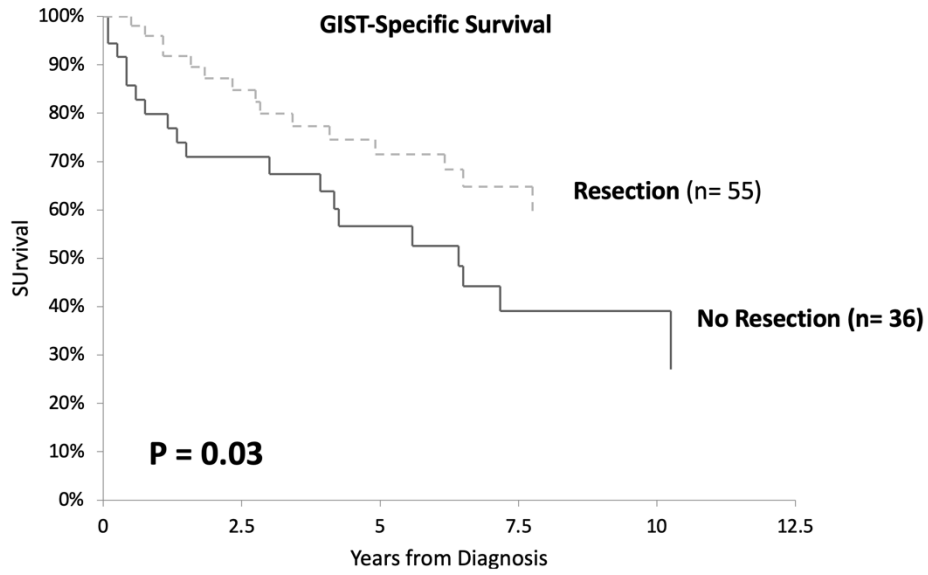
Sharma *et al…Sicklick, Clin Cancer Res*, 2022

Metastatic Disease - Debate

Palliation Resection only (Weldon *et al.*, *JCO* 2017)
vs.
Selective Resection (Fero *et al.*, *JAMA Surgery* 2017)

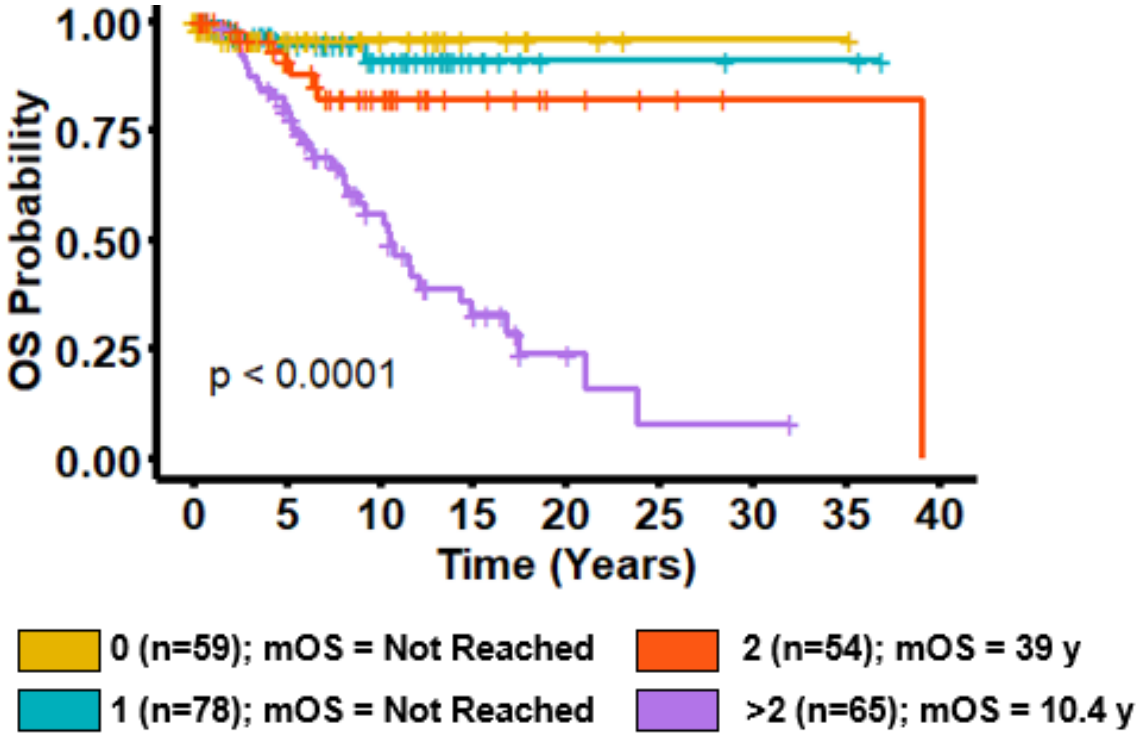
Weldon et al., showed in a study of 76 patients under 19 yo with WT-GIST diagnosis that there was an association between repeated surgical resections and decreased event-free survival.

SEER Subset analysis of AYA patients with metastatic disease, stratified by resection.

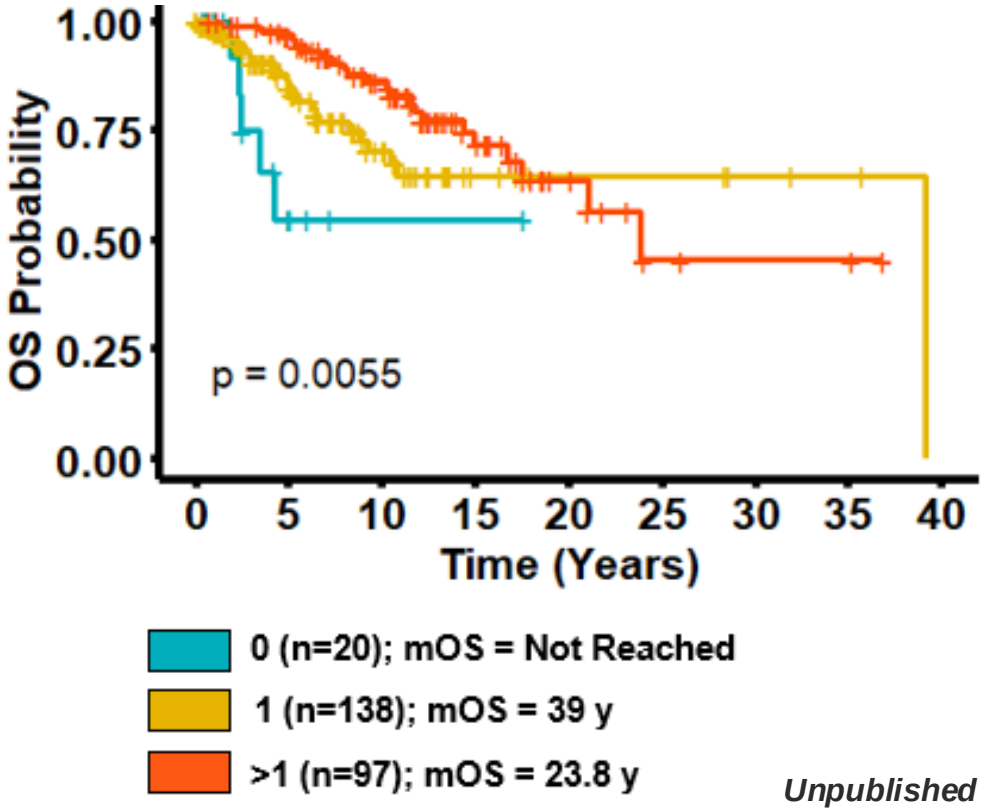


Surgery: Extent of Dz vs. Role of Resection?

Medications



Operations



Unpublished Data

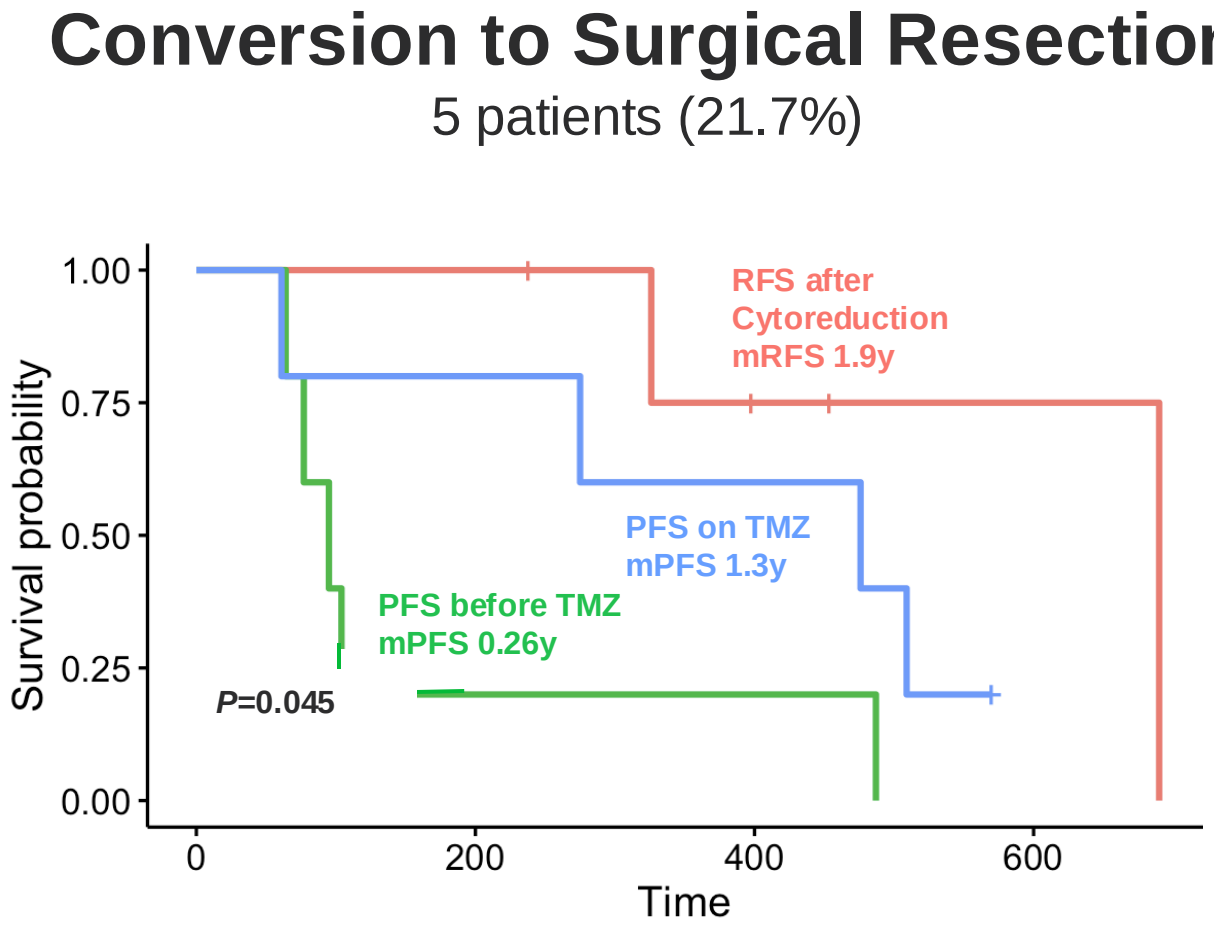
Surgical resection may play a role in managing this patient population?

Predictors of Worse OS

Variable	Univariate HR (95% CI)	*P*-value
≥29 yo vs. < 29 yo at diagnosis	2.36 (1.32-4.21)	0.004
Male vs. Female	2.51 (1.43-4.42)	0.001
Regionally advanced or metastatic disease vs. localized at diagnosis	1.81 (1.04-3.16)	0.034
Sunitinib	7.25 (3.26-16.10)	<0.001
Regorafenib	3.27 (1.79-5.97)	<0.001
Temozolomide	3.576 (1.40-9.16)	0.008
No Surgery vs. Surgery	2.831 (1.068-7.506)	0.036

Unpublished Data

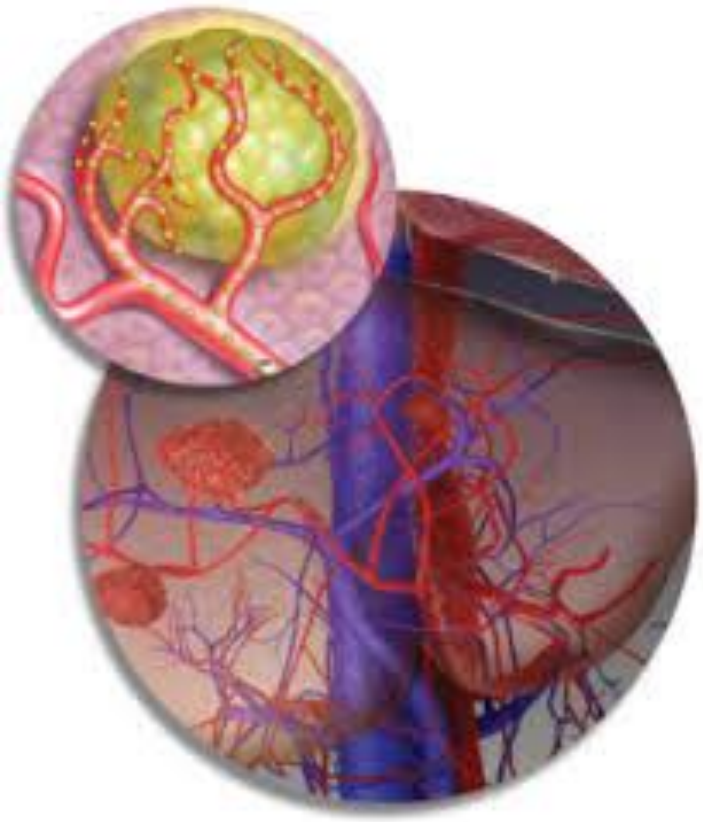
TMZ: Better Drug Therapies May Open Doors for More Extensive Surgery



Other Local Therapies…Selective Internal Radiation Therapy (SIRT) with Yittrium-90 Spheres

- To date, SIRT has not been evaluated in patients with SDH-deficient GIST

- This case series describes the long-term outcomes of patients treated with Y-90 SIRT for SDH-deficient GIST hepatic metastases in the **U.S., U.K. and Germany**



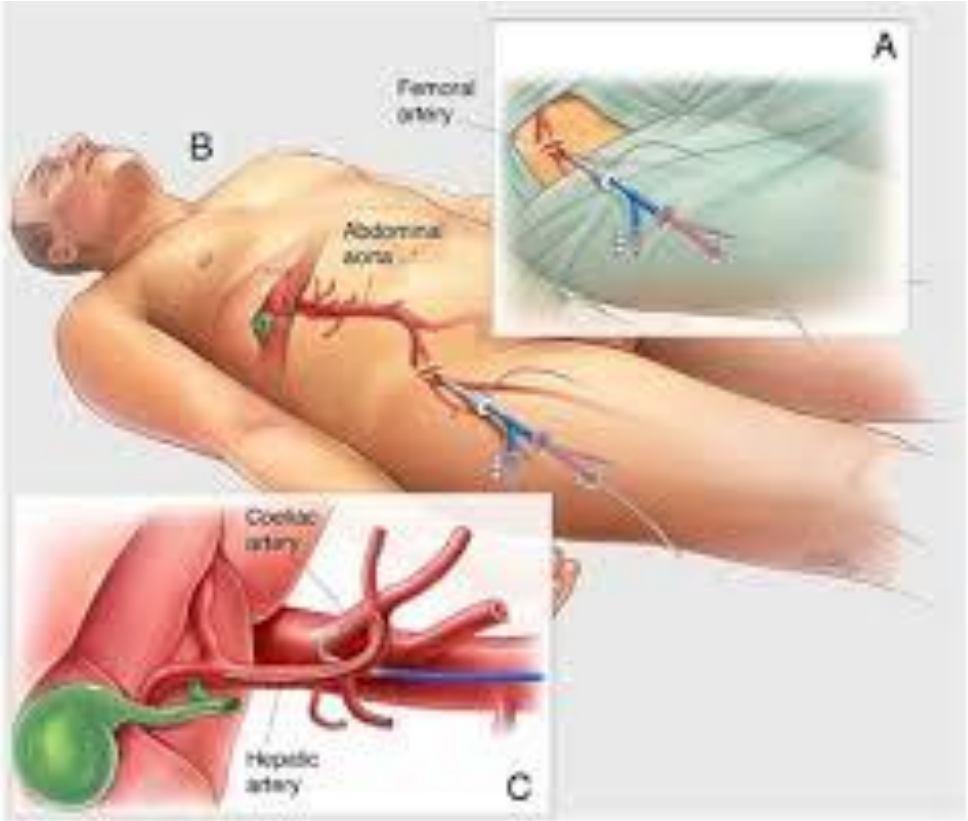
Demographics & Treatment History

- 10 patients: 70% F vs. 30% M
- Mean age at SIRT: 23.5 years (range 17-56)
- Germline mutations
  - *SDHA* (N=4, 40%)
  - *SDHB* (N=3, 30%)
  - *SDHC* (N=3, 30%)
- 9/10 patients had previously undergone partial gastrectomy ± additional abdominal cytoreductive surgeries prior to SIRT and were deemed to have unresectable liver metastases.
- 7/10 patients received prior systemic therapy (mainly TKIs)

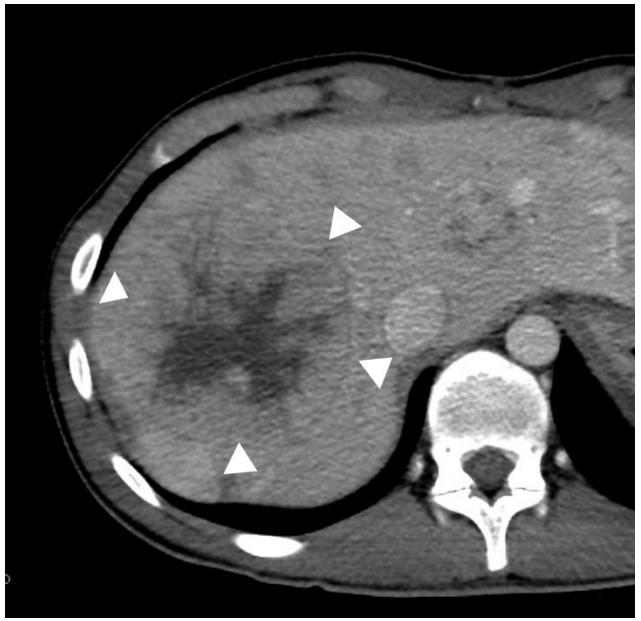
Treatments and Complications

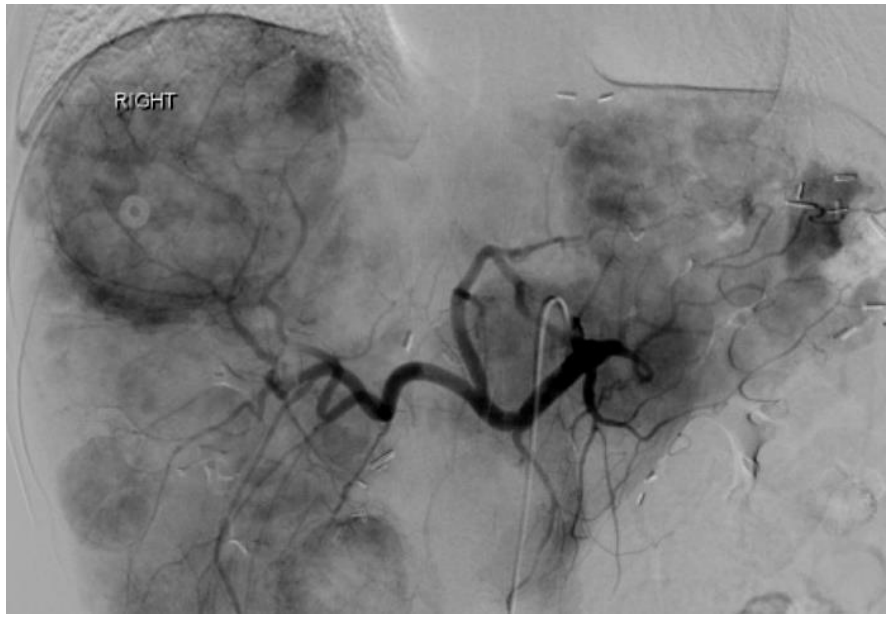
- Treatments
  - Unilobar: 3 (30%)
  - Bilobar: 7 (70%)

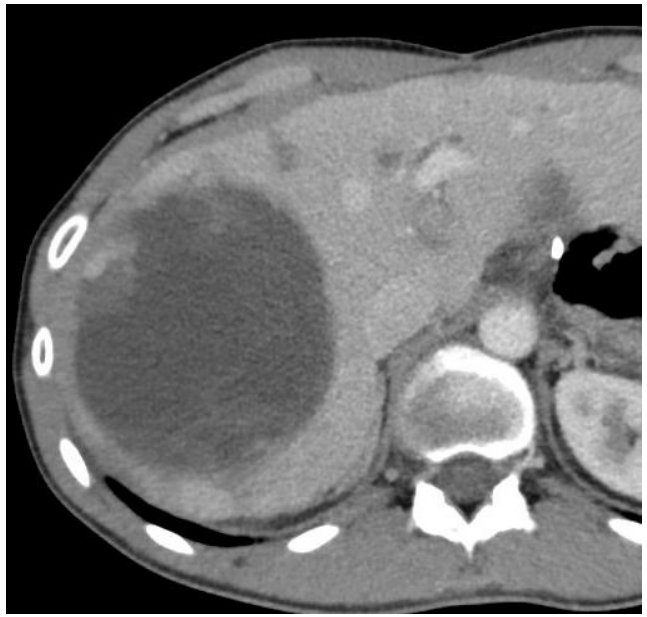
- Complications:
  - 1 cholecystitis, which required cholecystectomy.
  - No additional CTCAE v5 grade 3+ adverse events



SIRT for SDH-deficient GIST: Right Hemi-liver SIRT

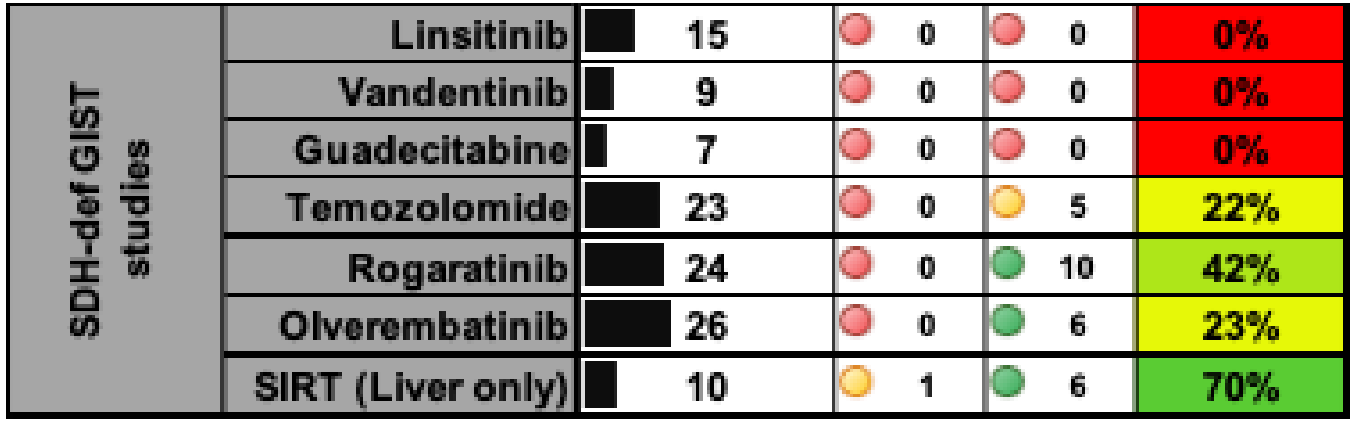






Radiologic Outcomes by RECIST in the Liver

- Median follow up time of 45 months (range: 10-82 mos)
  - 100% clinical benefit rate
  - 70% best ORR



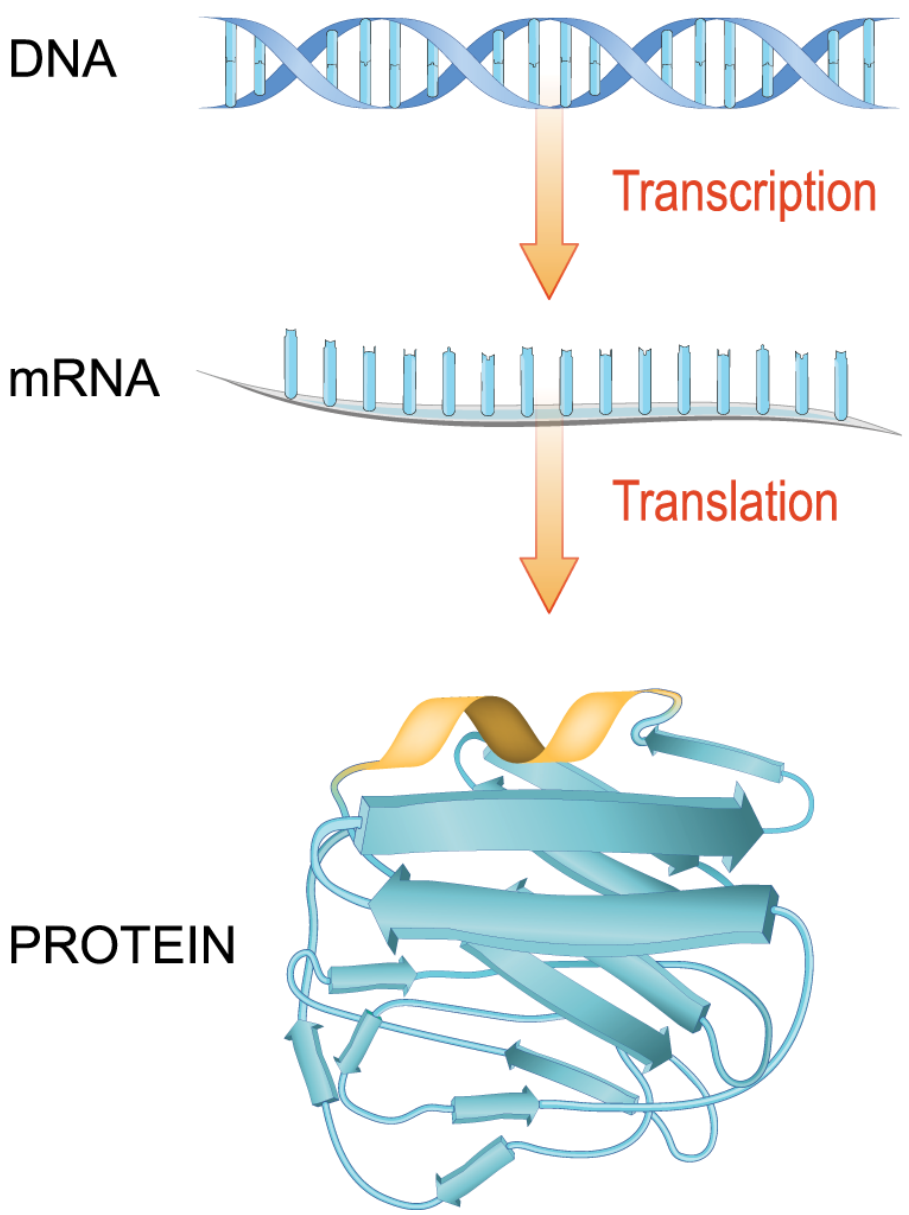
- In long-term follow up after SIRT
  - No disease progression has been observed within the treated portions of the livers.

CTOS 2024; Publication pending submission

Central Dogma

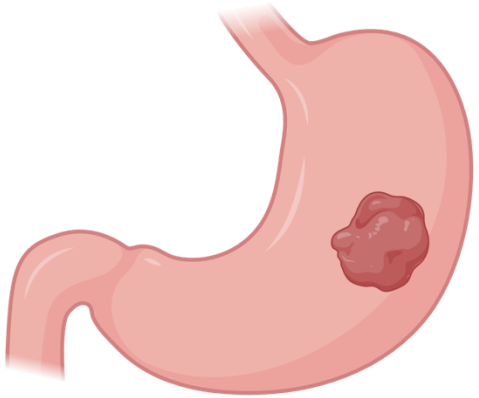
&

The Future



Approach to Better Study Personalized Prognostication

Collected 22 SDH-def GIST samples

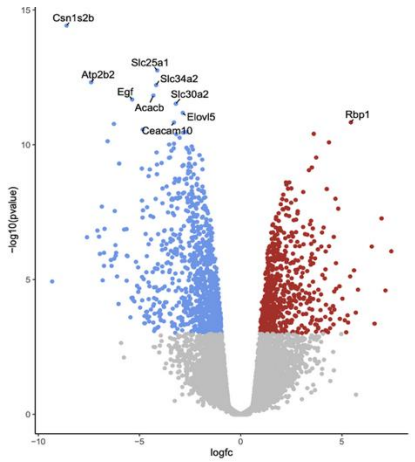


snRNAseq on 22 samples

Identified cell populations & defined their gene expression profiles

Downstream Analyses

Differential Gene Expression



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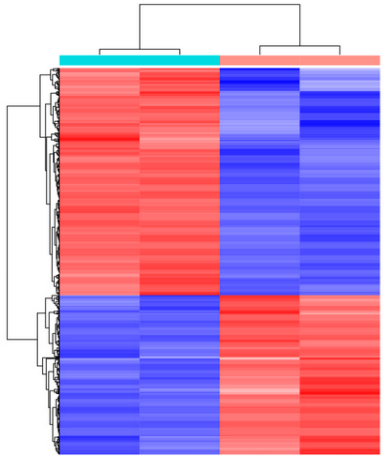
Identification of Transcriptomic States



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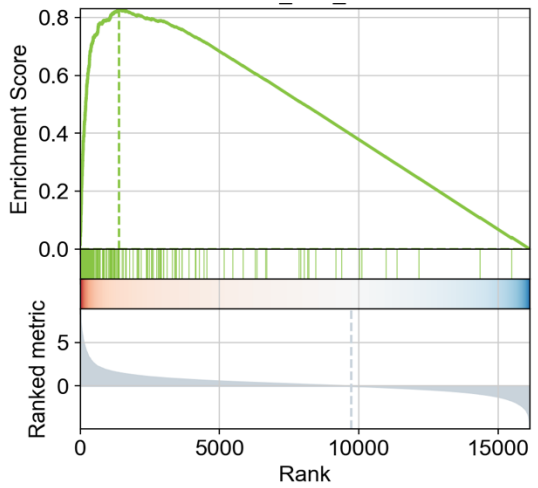
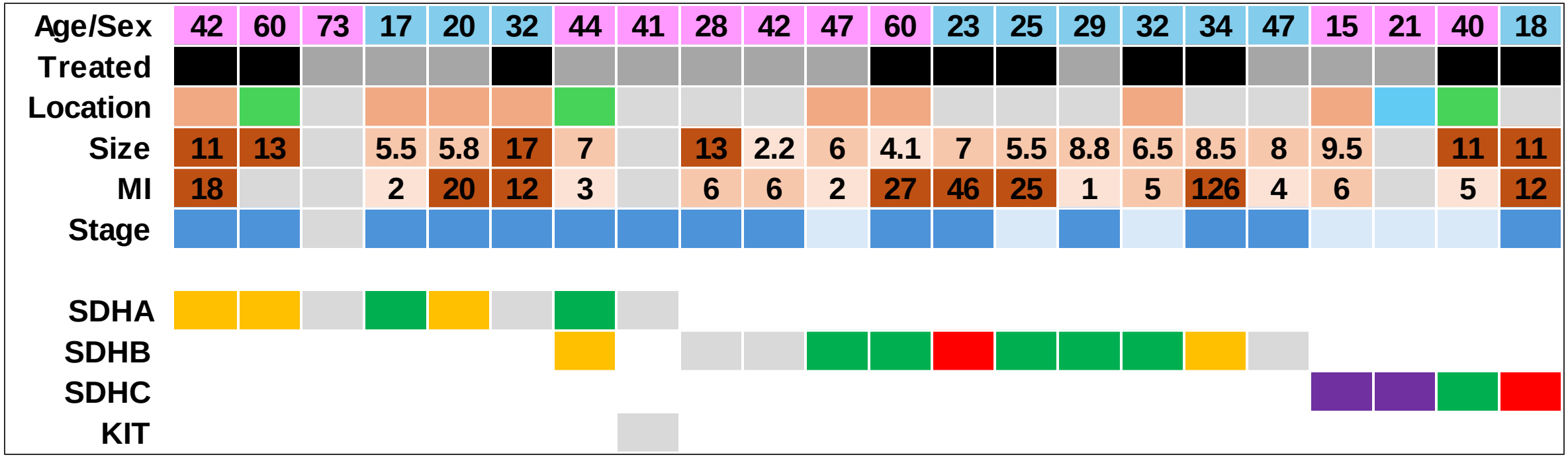
Characterization With GSEA



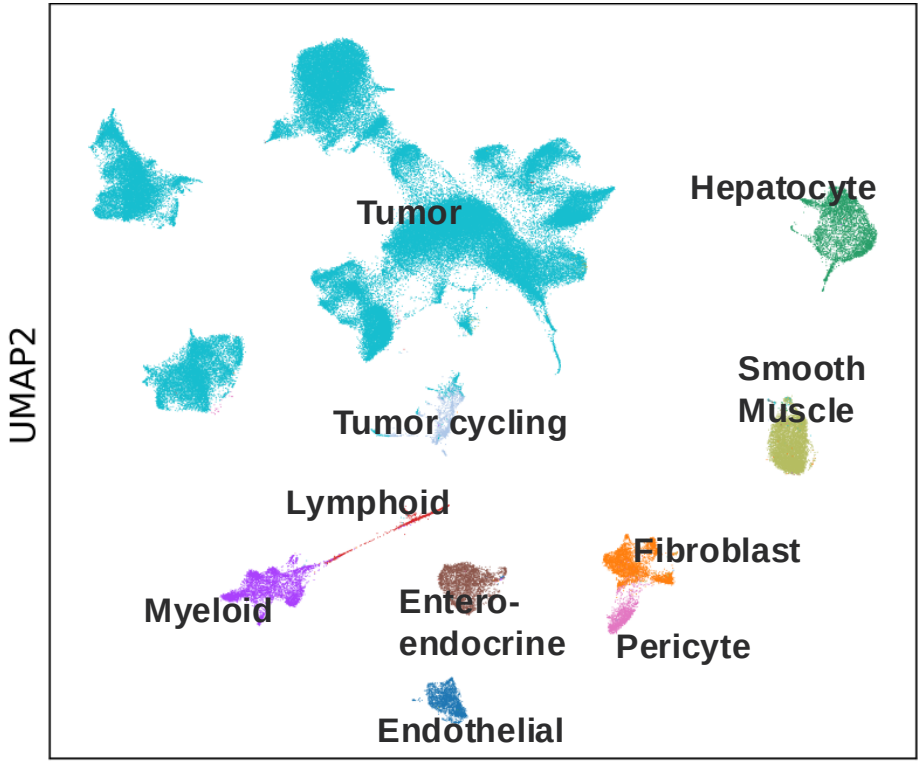
GSI GIST Support International

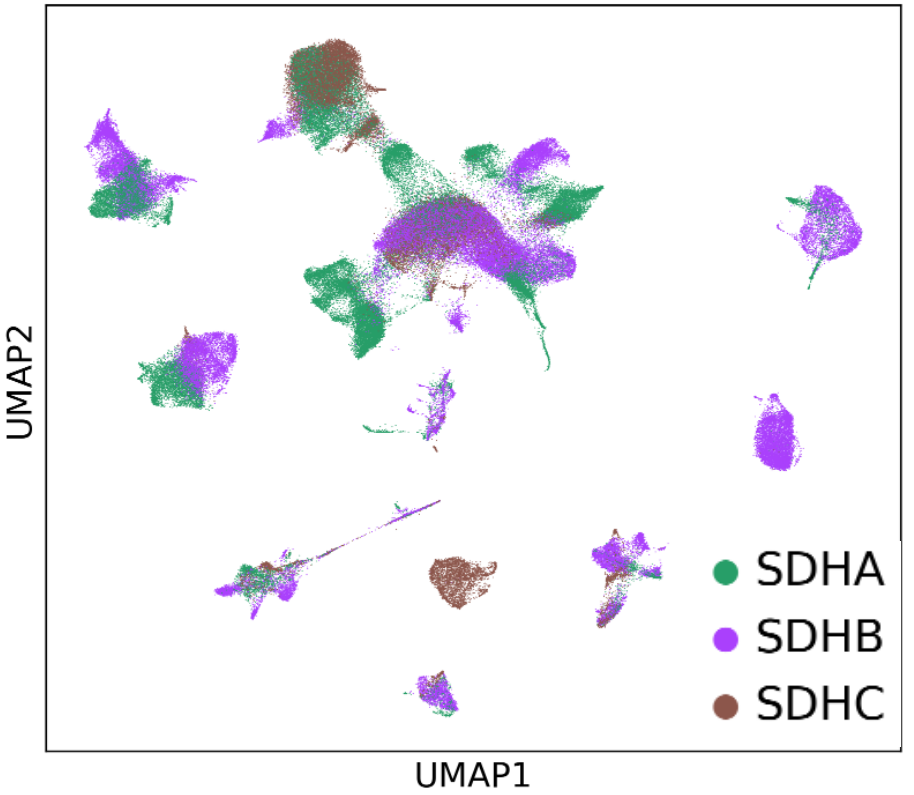
Co-mutation Plot of 22 SDH-def Samples

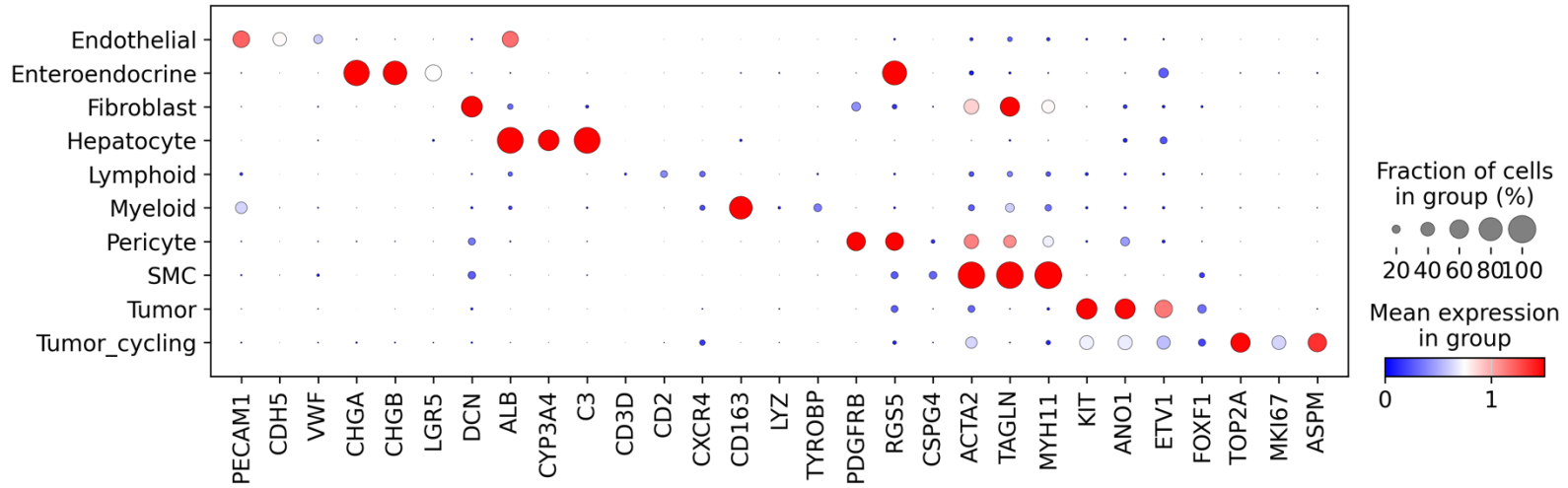


GIST Support International

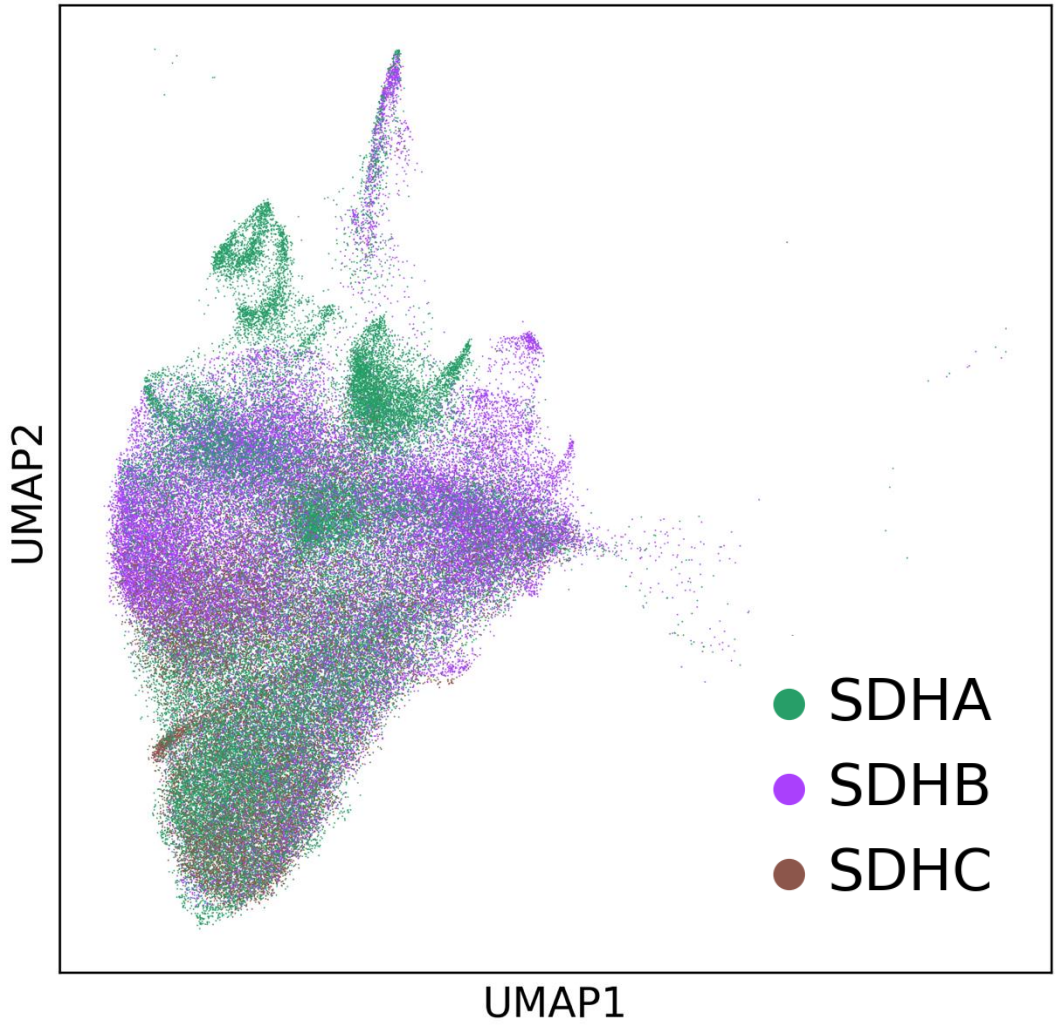
Single Nucleus RNA Seq Identifies 11 Cell Types

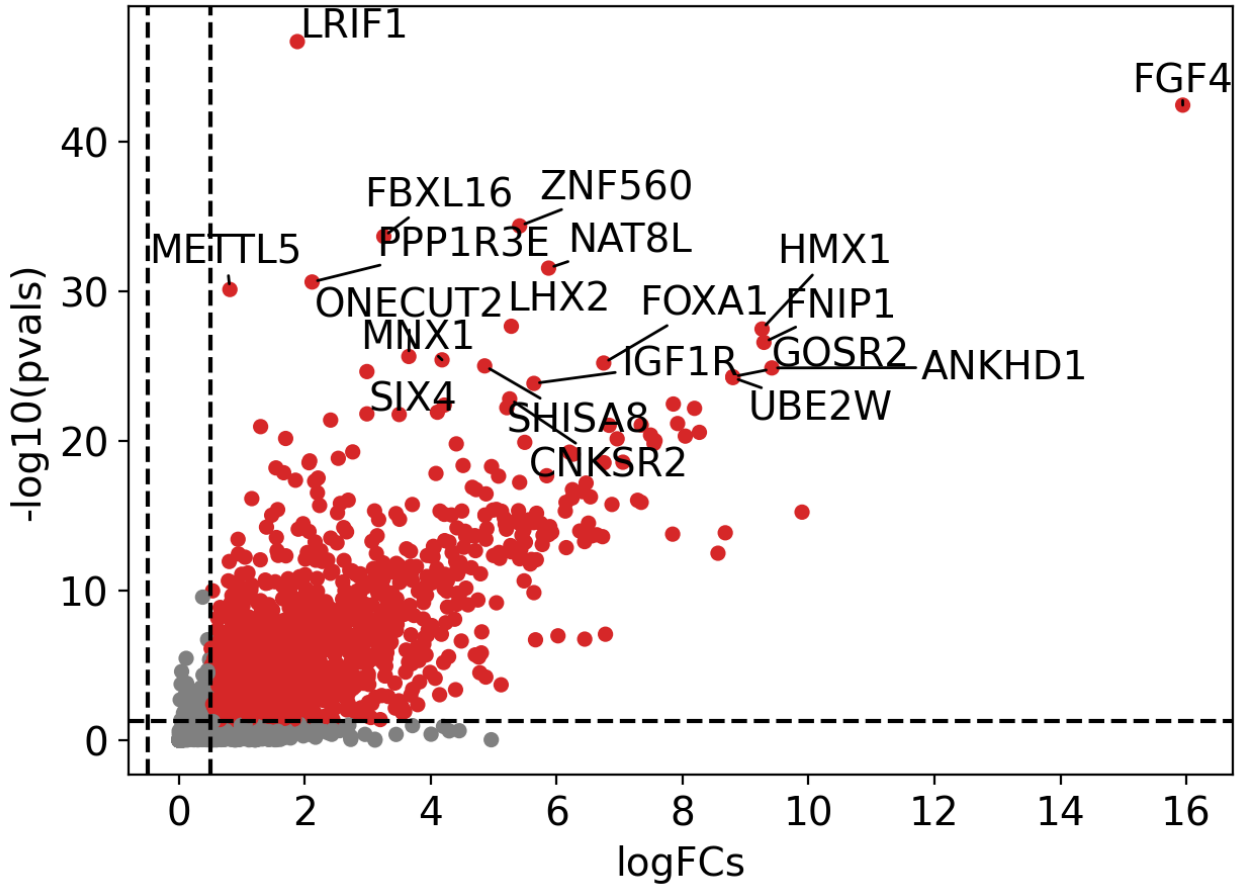






Differential Gene Expression of SDH-def GIST Tumor Cells



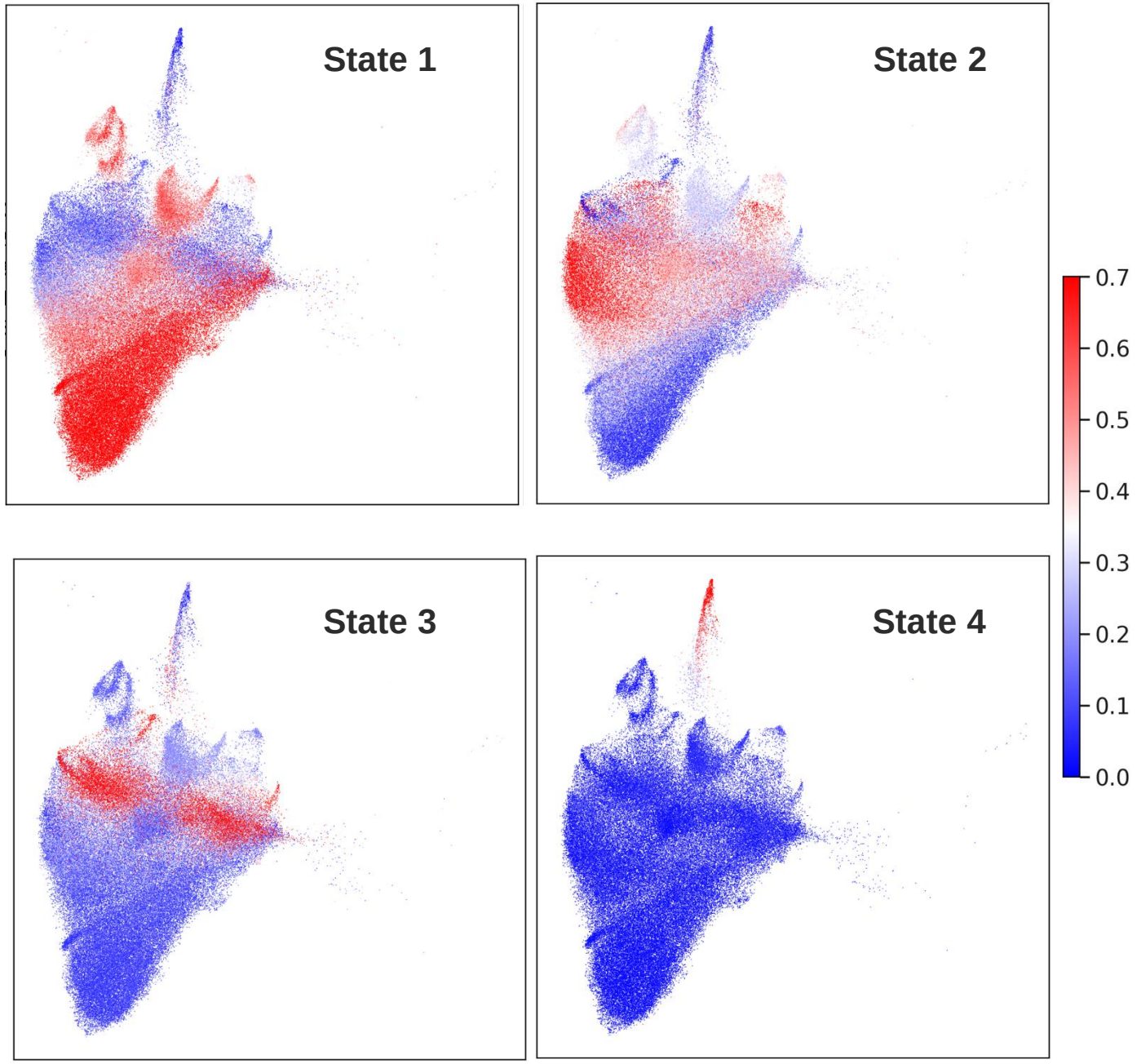


Differential Gene Expression of SDH vs KIT mutant GIST

Identification of Transcriptional Programs

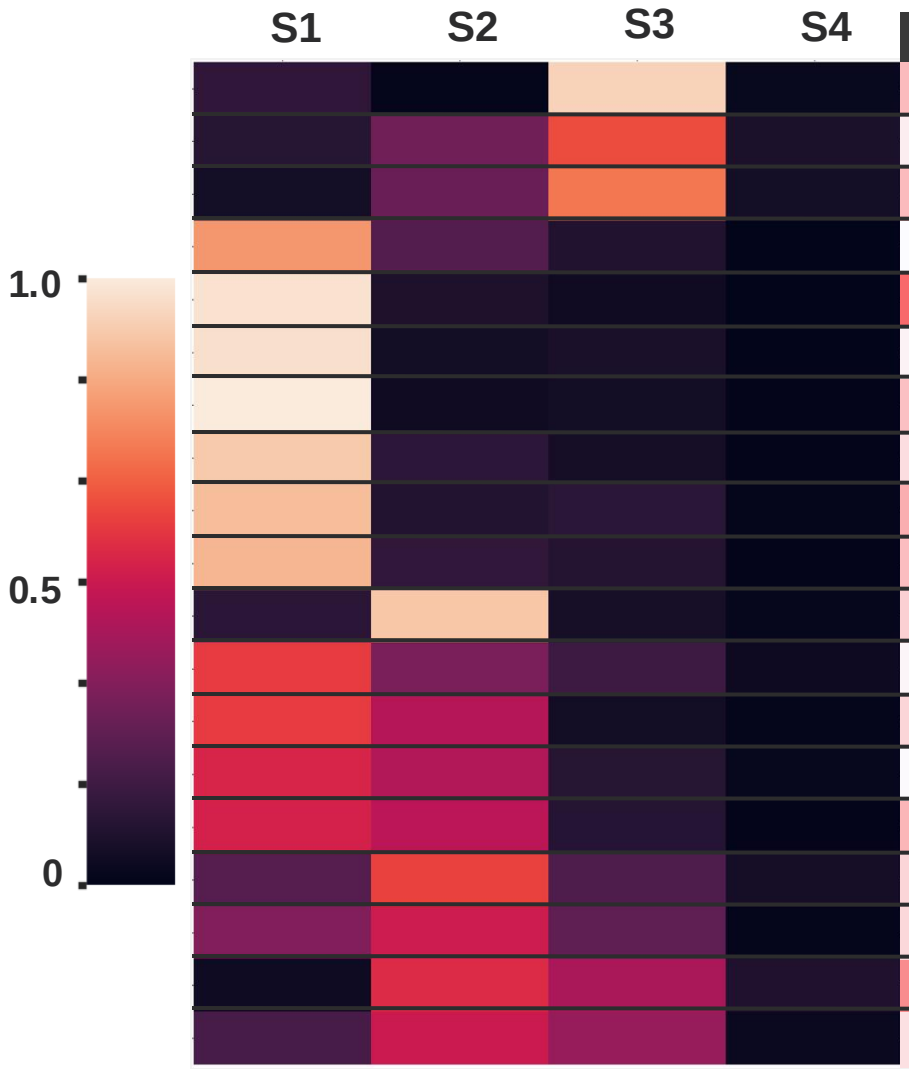
- Transcriptional programs were identified using a machine learning algorithm (Non-negative Matrix Factorization)

- **4 unique programs were identified**



Transcriptional Programs Provide Clinical Insights

- **S1: Inverse association with mitotic index (p=0.03)**
- **S4: Direct association with mitotic index (p=0.01)**
- **S3: Association with lines of therapy (p<0.01)**

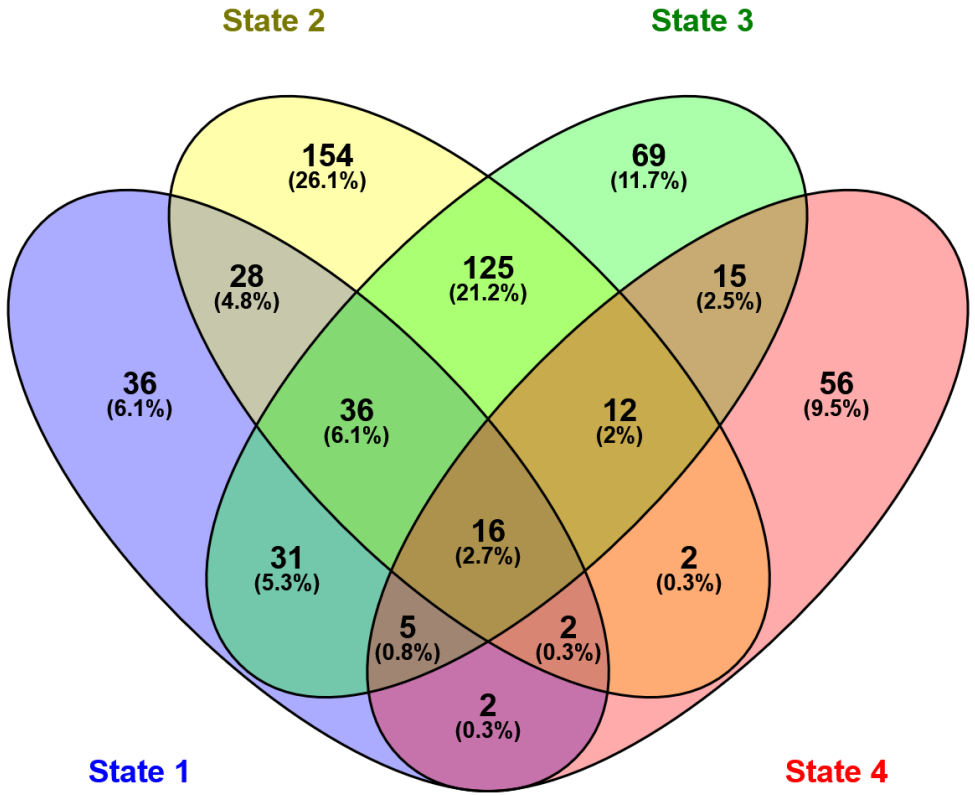


Age	Sex	Mut	Met	Size	MI	Tx
42	F	SDHA	yes	11	18	3
23	M	SDHB	yes	4.3	200	3
42	F	SDHB	yes	8.9	27	5
17	M	SDHA	yes	5.5	2	2
73	F	SDHA	no			1
21	F	SDHC	no			0
40	F	SDHC	no	2.5		1
29	M	SDHB	yes	8.8	1	3
47	M	SDHB	no	8	4	0
41	F	SDHA	yes			3
34	M	SDHB	yes	8.5	126	1
20	M	SDHA	yes	5.8	20	
32	M	SDHA	yes	17	12	1
18	M	SDHC	yes	11	12	1
44	F	SDHA	yes	7	3	0
32	M	SDHB	yes	6.5	50	1
31	M	SDHB	yes	5.5	11	2
60	F	SDHA	yes	13		4
28	F	SDHB	yes	3	40	4

Gene Set Enrichment Analysis Characterizes Transcriptional Programs

- **State 1: Metabolic, oxidative stress**
- **State 2: Migration, invasion**
- **State 3: Neuronal-like**
- **State 4: Mitotically active**

- Conserved pathways include:
  - KIT signaling
  - FGF signaling
  - ERBB signaling



Pre-ranked GSEA was performed using Hallmark, KEGG, and Reactome pathways. FDR < 0.05 was considered significant

Summary

- Genomics is broadening our understanding of GIST drivers, especially in non-*KIT/PDGFRA*-mutant GIST

- Just in the last 5+ years, we have advanced the science of SDH-deficient GIST to identify 4 novel therapies (TMZ, FGFR inhibitor, olverembatinib, Y-90 SIRT)

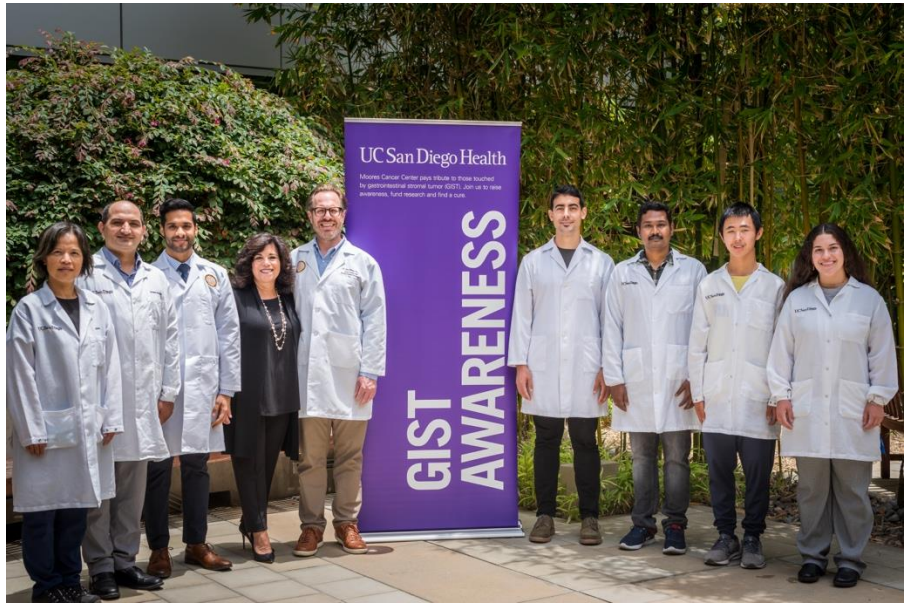
- Better therapies may create opportunities for increasing the role of surgical cytoreduction in patients with metastatic SDH-deficient GIST to change the natural history of a patient's disease

Summary

- Machine learning (i.e., Artificial Intelligence) has identified 4 unique transcriptional programs driving SDH-deficient tumor behavior.

- Further characterization of this tumor cell heterogeneity of SDH-deficient may help with:

  1. Determining prognosis &y clinical behavior (i.e., predicting indolent vs. aggressive biology)
  2. Identifying patients who may benefit from specific treatment(s) or drug combinations
  3. Identifying new therapies for investigation



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Patients & Families

THANK YOU!

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