GIST 101

Dr. Elizabeth Davis

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Elizabeth Davis, M.D.

July 10, 2026

Conflicts:

Research funding from Cogent, Cornerstone, Inhibrx, Actuate, and Pheast.

Consulting fees from GE, Aadi, Deciphera, SpringWorks, MJH LifeSciences.

What are sarcomas?

- Neoplasms arising from mesenchymal tissue
- Greek sarkoma “fleshy substance”- harmful connective tissue

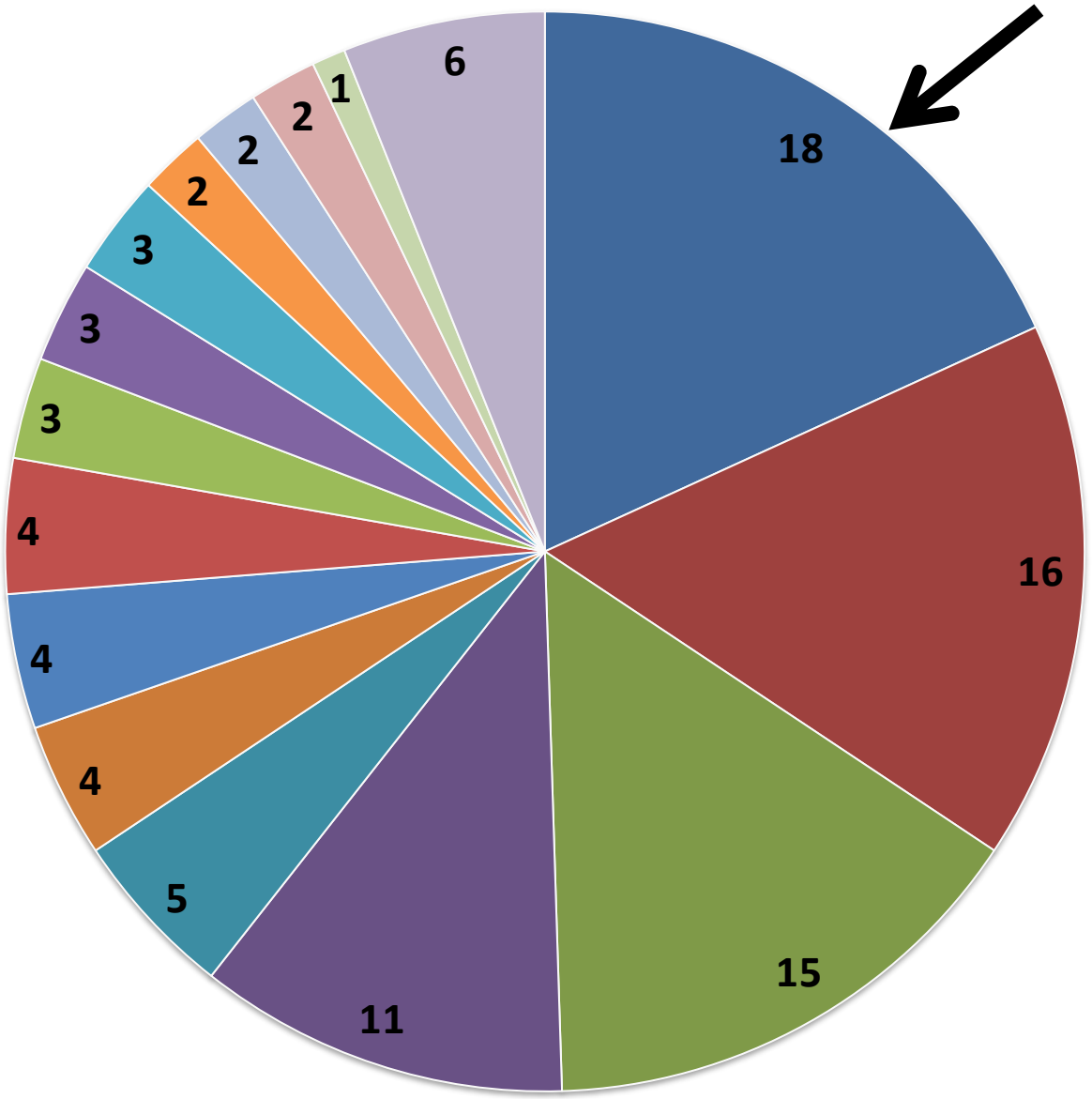
Soft tissue sarcoma (STS) (80%)

- 13,460 new cases/yr
- >100 subtypes
- All sites of body

Bone sarcoma (20%)

- 3,500 new cases/yr
- 3ish subtypes
  - Osteosarcoma
  - Ewing sarcoma
  - Chondrosarcoma
- Arises from bone

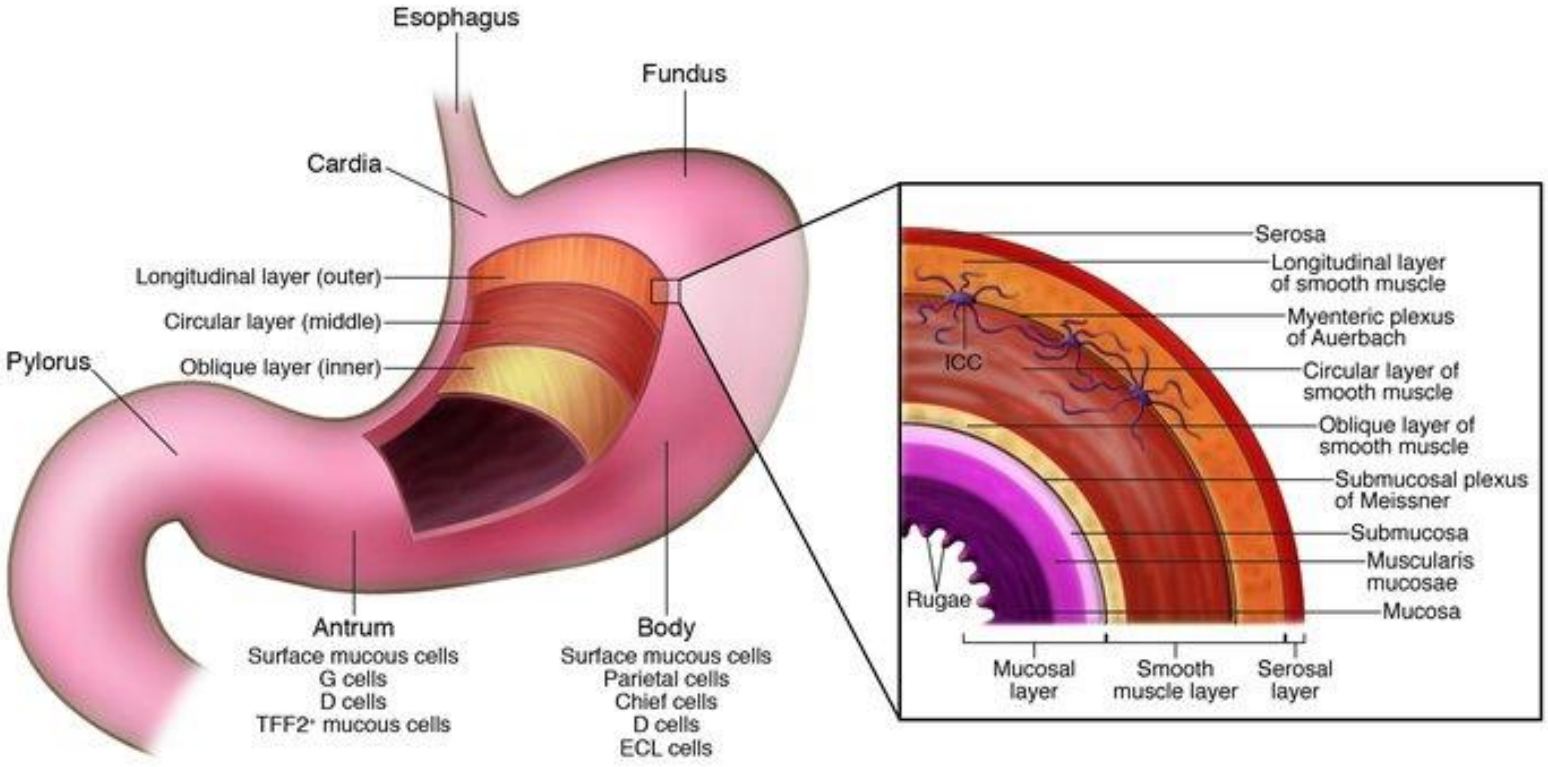
Adult sarcoma subtypes



- GIST
- Unclassified
- LPS
- LMS
- DFSP
- OS
- CS
- ES
- RMS
- Kaposi
- AS
- MFS
- SS
- ESS
- SFT
- Other

EJC 2014; 50:679–689.

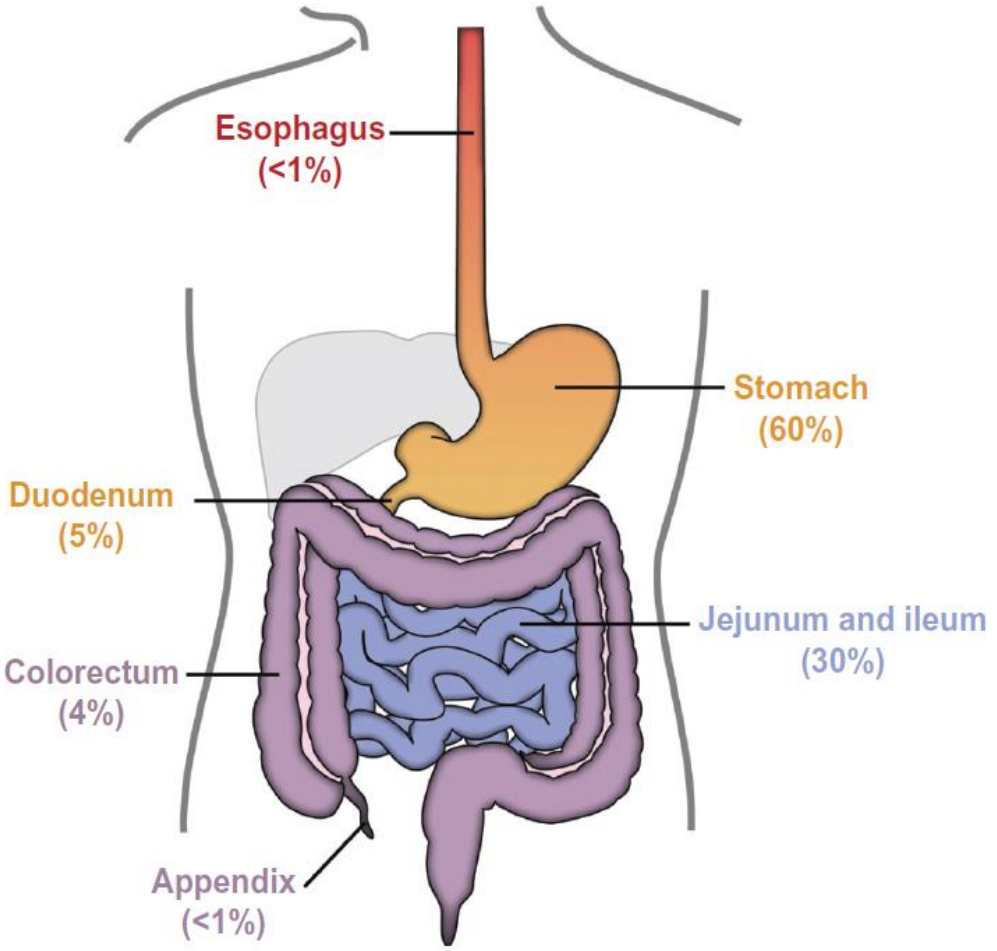
The origin of GIST



- Arises from mesenchymal tissue of the GI tract
- Originates from interstitial cells of Cajal
- 1998: KIT oncogene linked to GIST, near universal expression of KIT (CD117) in GIST

J Clin Invest DOI: 10.1172/JCI30491
Science, 279 (1998), pp. 577–580.

Epidemiology of GIST



Primary GIST anatomic locations and relative frequencies.

- 5000-6000 cases/yr
- Med age 60yo
- M=F

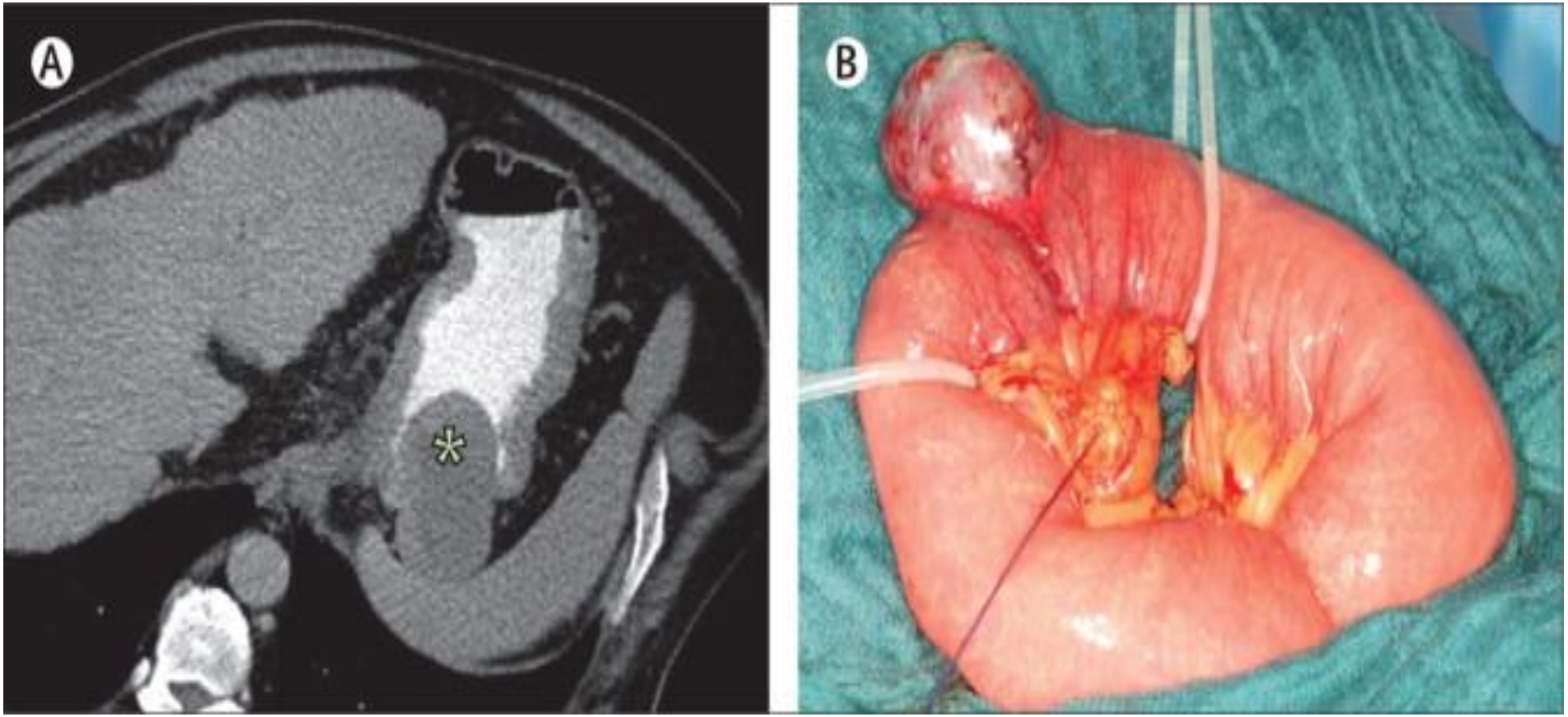
Etiology of GIST

- Sporadic
- Primary familial GIST syndrome
  - Heritable KIT mutations, multiple gastric and small bowel tumors
- Neurofibromatosis type 1
  - Intestinal GIST, often indolent
- Carney-Stratakis syndrome
  - GIST and paraganglioma
  - germline mutation in SDHB, SDHC, or SDHD
  - mean age 23yo, gastric, multifocal, usually indolent course
- Carney's triad
  - Pulmonary chondroma, GIST, paraganglioma
  - non-hereditary, young women, SDHB deficient
  - usually gastric, multifocal

Work-up for GIST

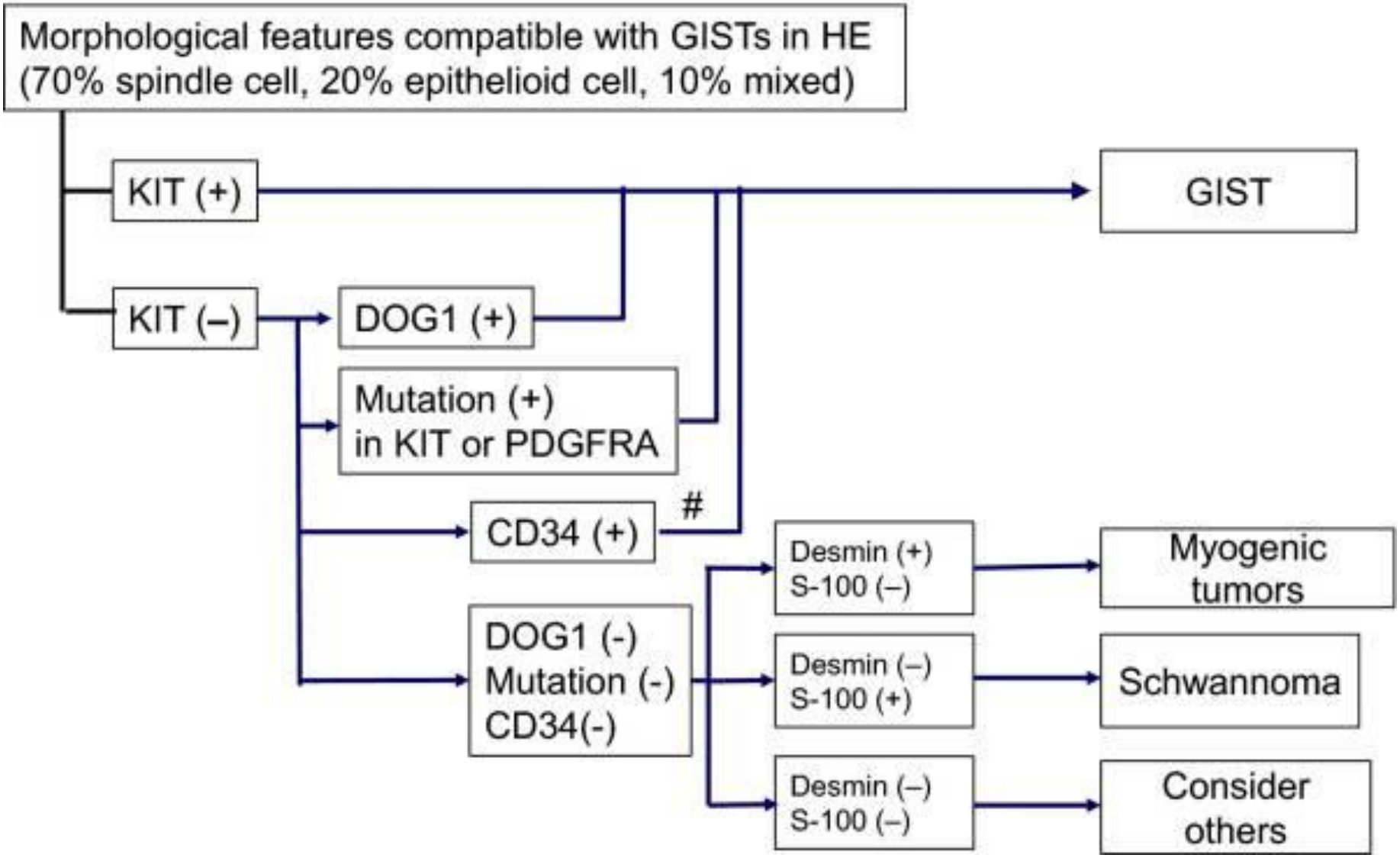
- CT AP with contrast (or MRI)
- Biopsy
  - Endoscopically of primary mass OR
  - US/CT-guided liver biopsy of metastasis
- Mutational testing of tumor

Images of GIST



Lancet. 2013, 973–983

Molecular pathology



Gastric Cancer. 2016; 19: 3–14.

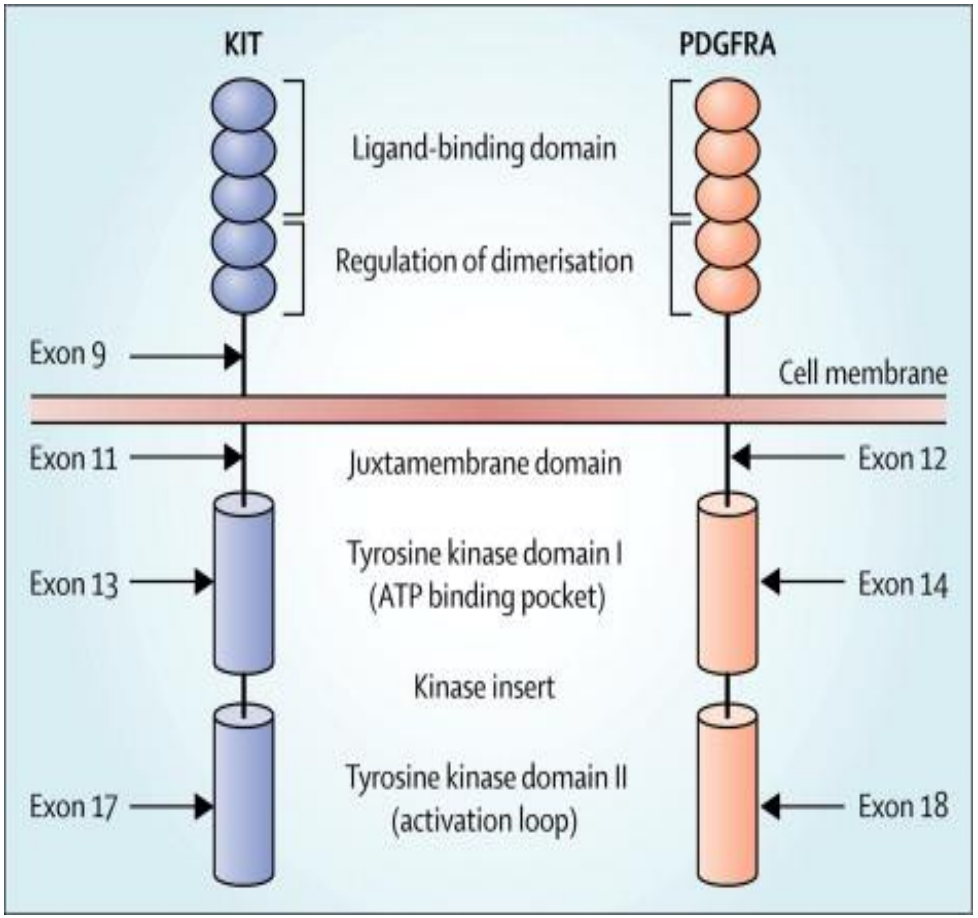
Immunohistochemistry (IHC) *vs*. Mutational testing:
different tests, different questions, different answers

	Immunohistochemistry	Mutational testing
What it is:	**Staining for the KIT protein**	**DNA sequencing of the *KIT* gene**
What it tests for:	**expression of KIT protein by the tumor cells**	**mutations in the *KIT* gene in the tumor cell DNA**
What it tells us:	**is the tumor GIST? (often, this simply confirms the diagnosis)**	**is the tumor a *KIT*-mutant GIST (and, if so, what is the *KIT* mutation?)***
What it requires:	**a tumor sample (biopsy or surgery)**	**a tumor sample (*e.g.*, FFPE: Formalin-Fixed Paraffin-Embedded)**
Will the test be performed by the pathology lab?	***always***	***sometimes***

*If no mutation is found in the *KIT* gene, further mutational testing can be performed.

GIST Genomics

- KIT mutations (80-85%)
  - Exon 11 (65-70%)
  - Exon 9 (8-10%)
  - Exon 8, 13, 17 (all rare)
- PDGFRA mutations (5-10%)
  - Exons 18 (80%), 12, and 14
  - Exon 18 D842V confers resistance to imatinib
- Wild-type (10-15%)
  - Loss of function mutations in SDH or loss of SDHB expression
  - BRAF, NF1, HRAS, NRAS

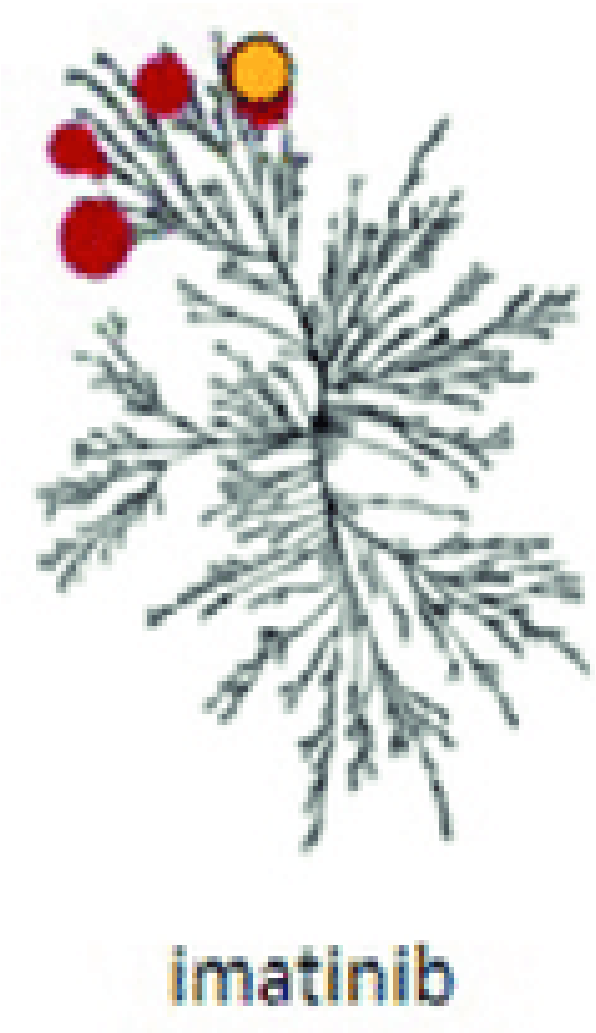


Lancet, 2013, 973–983

Treatment of GIST pre-imatinib

- Surgery
- Chemo but GIST is ***not*** chemoresponsive.
- Median survival
  - Metastatic disease: 20 months
  - Recurrent disease: 9-12 months
- Other treatment strategies were needed. . . . .
  - Targeting c-kit?

Imatinib



- Selective inhibitor of protein tyrosine kinases
  - Intracellular ABL
  - Chimeric BCR-ABL fusion
  - Transmembrane receptor KIT
  - Platelet-derived growth factor receptors
- Highly active in GIST, CML and Ph+ leukemias

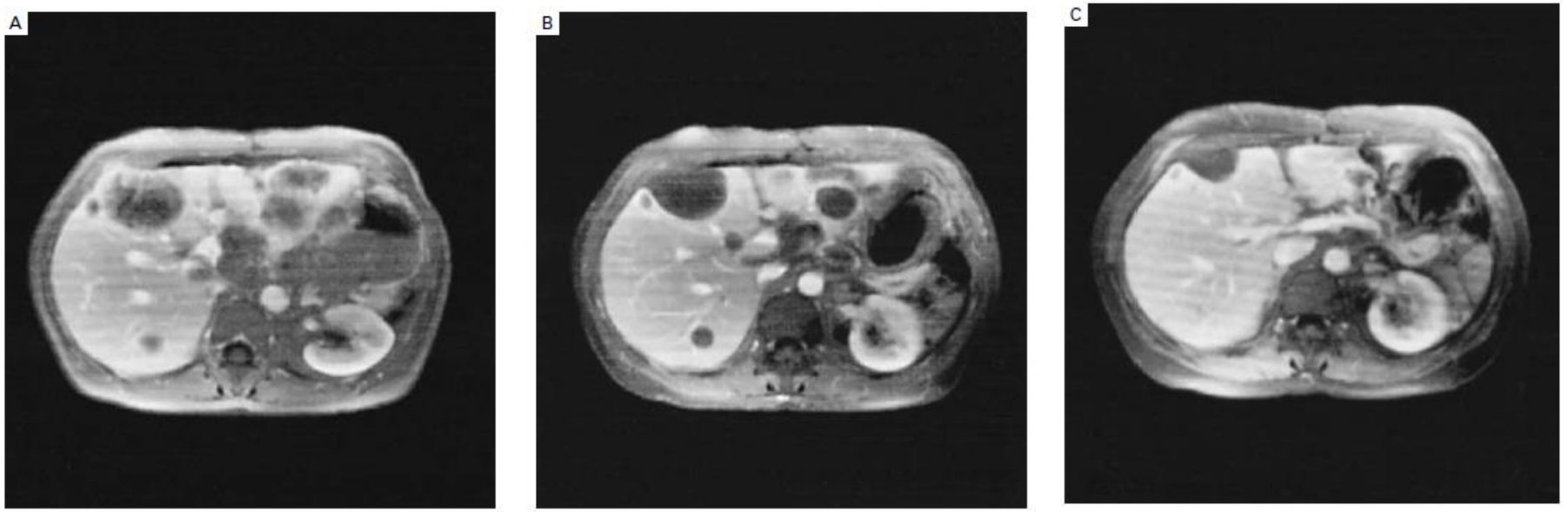
Brief Report

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

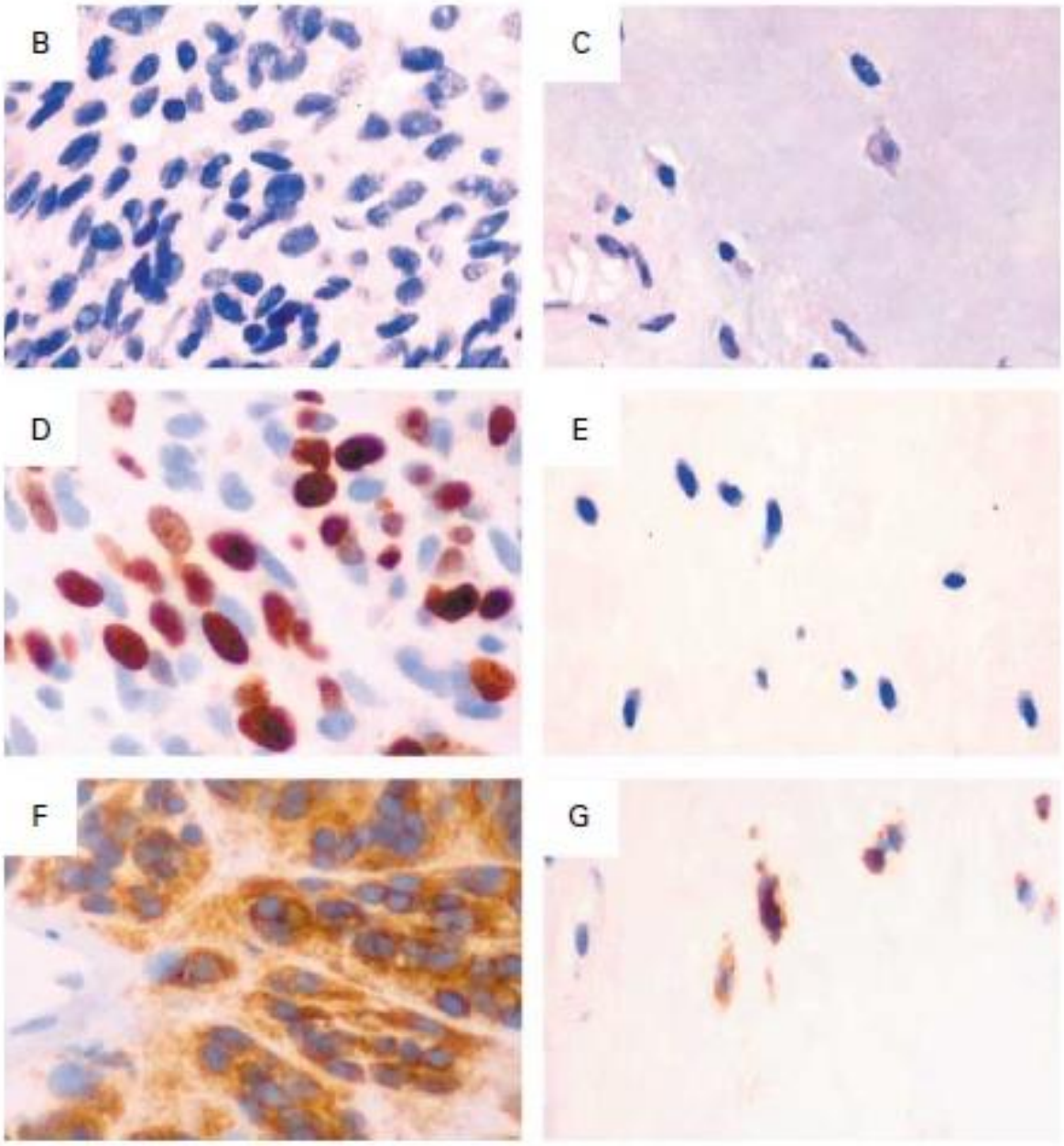
Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

Treatment pre-imatinib

-10/1996: surgery, c-kit mutation in exon 11.
-2 and 9/1998: surgery
-1998/99: doxorubicin, ifosfamide, dacarbazine x 7 -> PD
-March 1999: surgery
-1999/2000: Thalidomide/interferon -> PD
-March 2000: STI571 (imatinib) 400mg daily



N Engl J Med. 2001 Apr 5;344(14):1052-6.



N Engl J Med. 2001 Apr 5;344(14):1052-6.

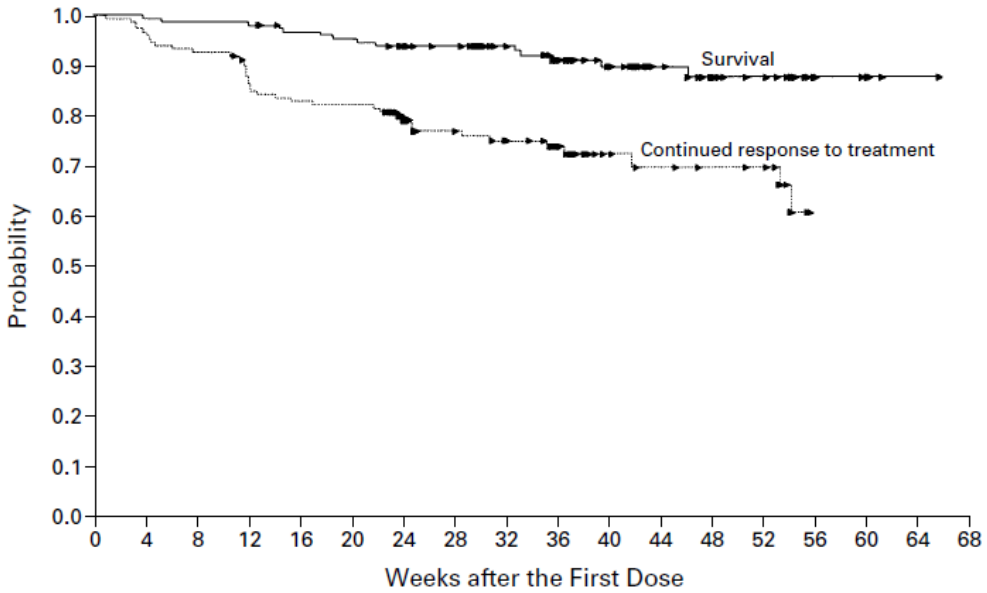
EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D., ANNICK D. VAN DEN ABBEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D., DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D., STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.SC., BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D., CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

TABLE 2. RESPONSES TO IMATINIB IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS.*

BEST RESPONSE	400 mg (N=73)	600 mg (N=74)	EITHER DOSE (N=147)
		no. (% [95% CI])	
Complete response	0	0	0
Partial response	36 (49.3 [37.4–61.3])	43 (58.1 [46.1–69.5])	79 (53.7 [45.3–62.0])
Stable disease	23 (31.5 [21.1–43.4])	18 (24.3 [15.1–35.7])	41 (27.9 [20.8–35.9])
Progressive disease	12 (16.4)	8 (10.8)	20 (13.6)
Could not be evaluated	2 (2.7)	5 (6.8)	7 (4.8)

*CI denotes confidence interval.



- Median f/u: 63 mo.
- Median survival: 57mo. (20 mo. pre-imatinib)
- 9yr OS: 35%
- Better OS:
  - Female sex
  - Exon 11 mutation

NEJM 2002;347:472-80.
J Clin Oncol. 2008;26(4):620.

Imatinib after surgery

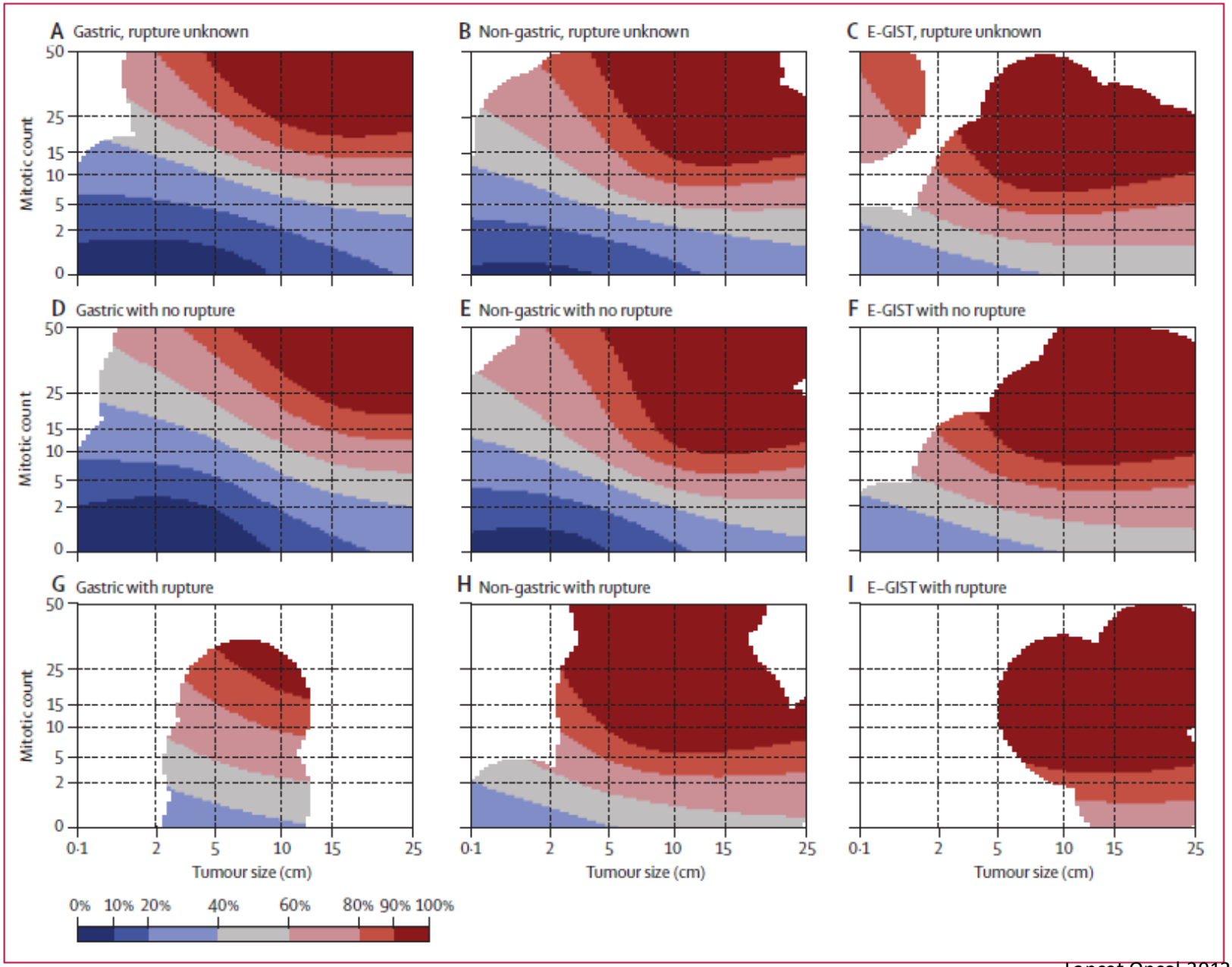
65yo woman presents with anemia and a palpable LUQ mass. CT AP demonstrates an 11-cm mass in the LUQ. Biopsy reveals GIST with 15m/50HPF. She undergoes surgical removal of her GIST. There is no rupture.

- ***What are prognostic factors that factor into recurrence risk after resection?***
- ***Is adjuvant therapy recommended?***

What are 4 prognostic factors that factor into recurrence risk after resection of GIST?

- Size
- Location
- Mitotic activity
- Rupture

GIST recurrence

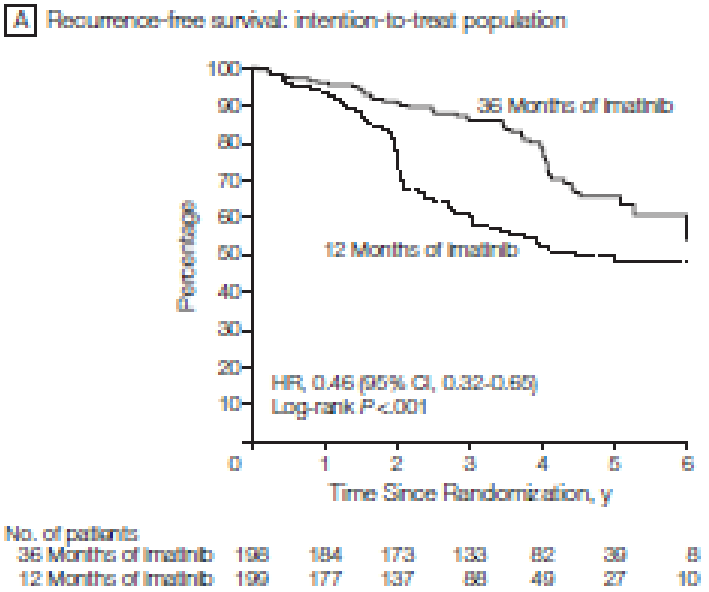


Lancet Oncol 2012;13: 265-74.

How long should she take imatinib?

- SSG XVIII
  - 400pts w/high-risk resected GIST
    - tumor >10cm
    - mitotic >10/50HPF
    - >5cm and mitotic >5/HPF
    - rupture
  - Imatinib 400mg daily 12 vs. 36 months
  - 1° endpoint- RFS
  - 2° endpoints- OS and safety

JAMA. 2012 Mar;307(12):1265-72.

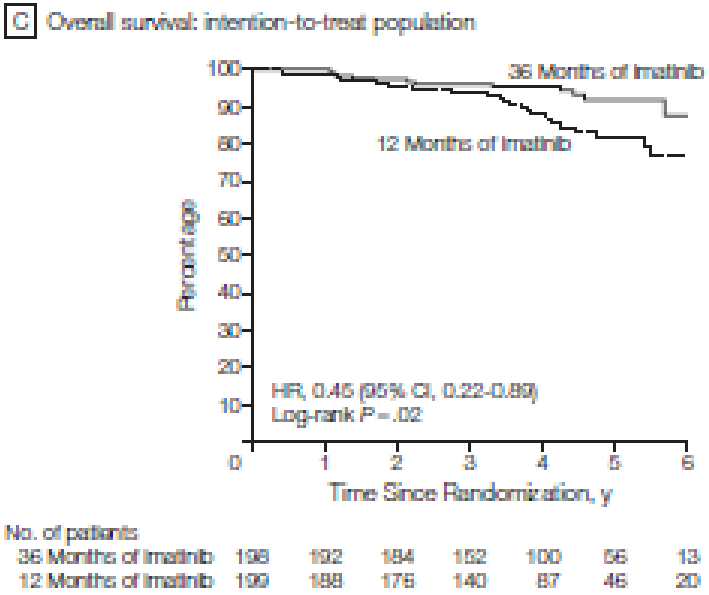


RFS 1 vs. 3 yr

5yr RFS: 48% vs 66%

HR 0.46 (0.32-0.65)

p<0.001



OS 1 vs. 3 yr

5yr OS: 82% vs 92%

HR 0.45 (0.22-0.89)

p<0.02

JAMA. 2012 Mar;307(12):1265-72.

Adverse events

Events	No. (%)					
	All Grades			Grade 3 or 4		
	12-mo Group (n = 194)	36-mo Group (n = 198)	*P* Value[a]	12-mo Group (n = 194)	36-mo Group (n = 198)	*P* Value[a]
Any event	192 (99.0)	198 (100.0)	.24	39 (20.1)	65 (32.8)	.006
Hematological						
Anemia	140 (72.2)	159 (80.3)	.08	1 (0.5)	1 (0.5)	>.99
Leukopenia	67 (34.5)	93 (47.0)	.01	4 (2.1)	6 (3.0)	.75
Nonhematological						
Periorbital edema	115 (59.3)	147 (74.2)	.002	1 (0.5)	2 (1.0)	>.99
Fatigue	94 (48.5)	96 (48.5)	>.99	2 (1.0)	1 (0.5)	.62
Nausea	87 (44.8)	101 (51.0)	.23	3 (1.5)	1 (0.5)	.37
Diarrhea	85 (43.8)	107 (54.0)	.04	1 (0.5)	4 (2.0)	.37
Muscle cramps	60 (30.9)	97 (49.0)	<.001	1 (0.5)	2 (1.0)	>.99
Leg edema	64 (33.0)	81 (40.9)	.12	1 (0.5)	2 (1.0)	>.99
Biochemical						
Elevated blood lactate dehydrogenase	84 (43.3)	119 (60.1)	.001	0	0	
Elevated serum creatinine	59 (30.4)	88 (44.4)	.005	0	0	

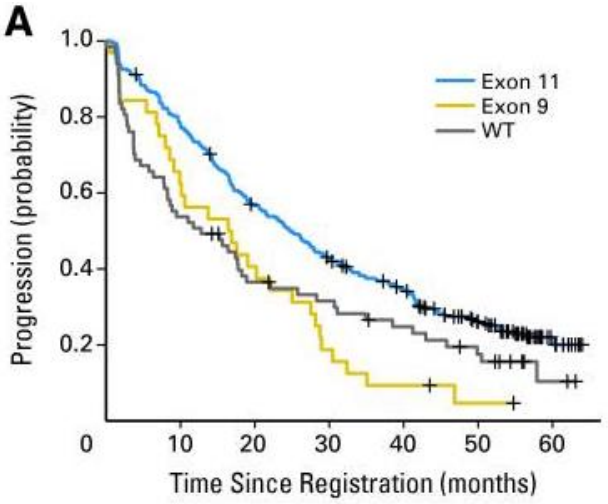
JAMA. 2012 Mar;307(12):1265-72.

Treatment of metastatic GIST after progression on imatinib

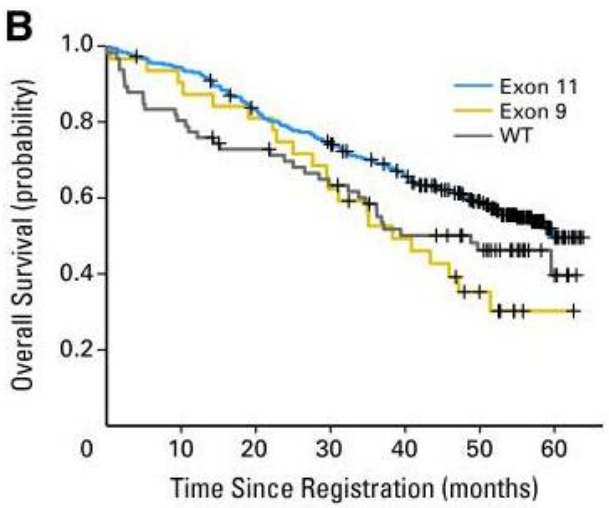
72yo man with metastatic small bowel GIST (exon 9 mutation) is being treated with imatinib 400mg daily. At his return visit, CT AP demonstrates marked progression of liver metastases. He has been compliant with imatinib 400mg.

- ***What is the most appropriate management strategy?***
  - Increase imatinib to 800mg
  - Start sunitinib
  - Start regorafenib
  - Start ripretinib

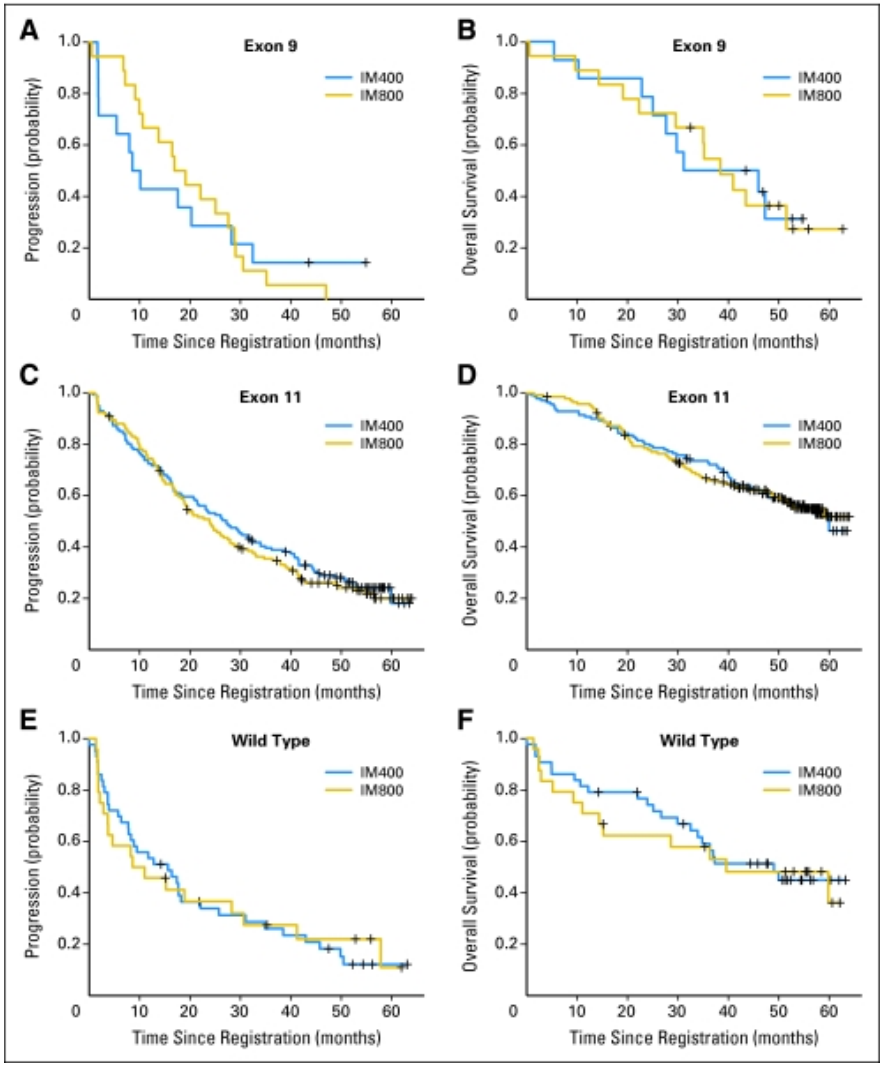
Does mutation matter?



Mut	TTP
11	24.7
9	16.7
WT	12.8



Mut	OS
11	60
9	38.4
WT	49



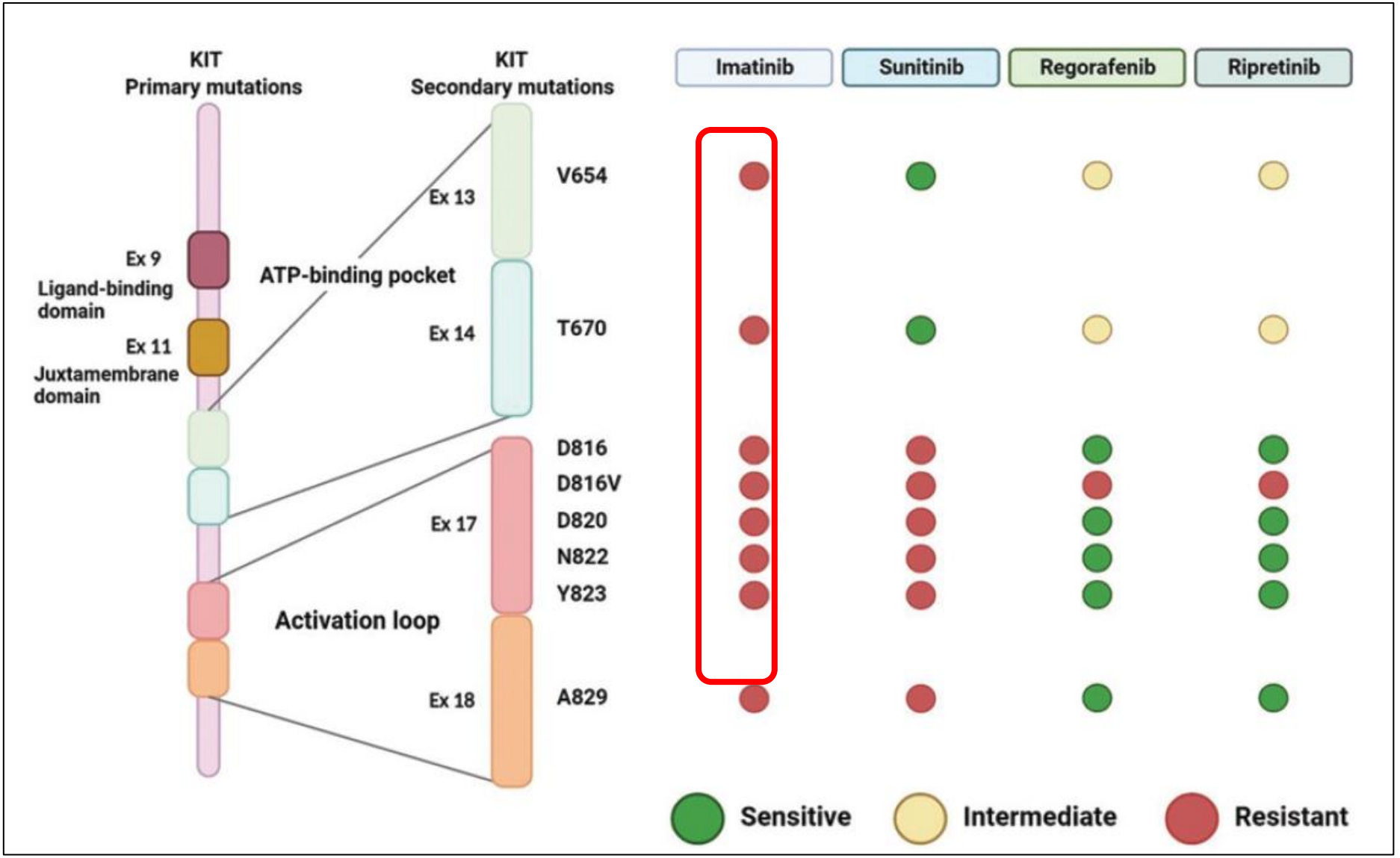
- Pts with PDGFRA D842V mutation are resistant to imatinib.
- Improved response rate in exon 9 treated with 800mg (67 vs 17%).

J Clin Oncol. 2008;26(33):5360.
Clin Cancer Res. 2012;18(16):4458.

Post-imatinib treatment

The patient responds to imatinib 800mg daily but then has further disease progression. He has a good PS and wants further therapy.

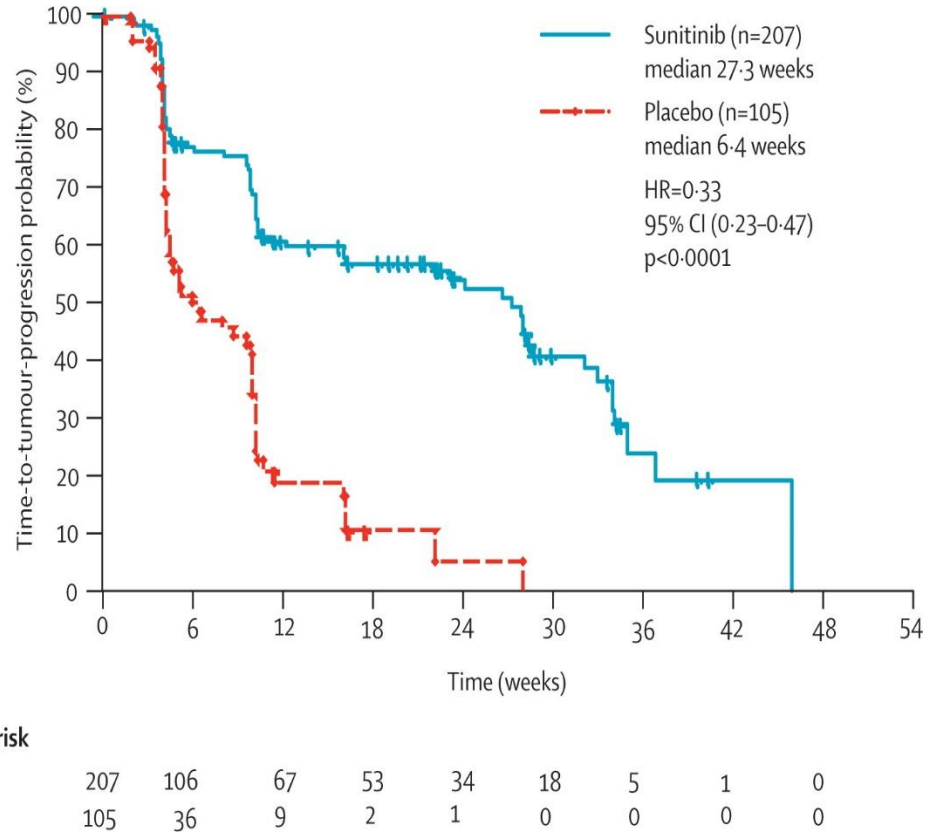
Imatinib resistance: secondary mutations in *KIT*



Cicala *et al.*, *Expert Opin. Investig. Drugs*, 2024

Sunitinib

Blocks *KIT*, *PDGFR*s, *VEGFR*s, *FLT3,* and *RET*



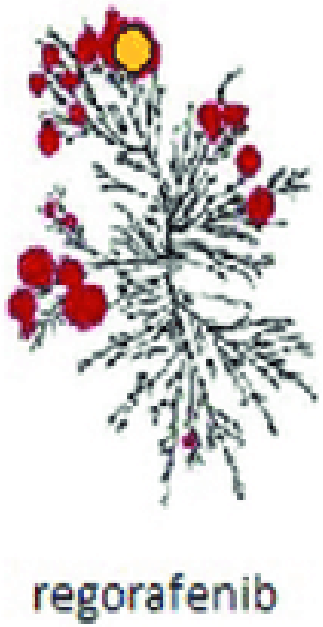
Number at risk

Sunitinib	207	106	67	53	34	18	5	1	0
Placebo	105	36	9	2	1	0	0	0	0

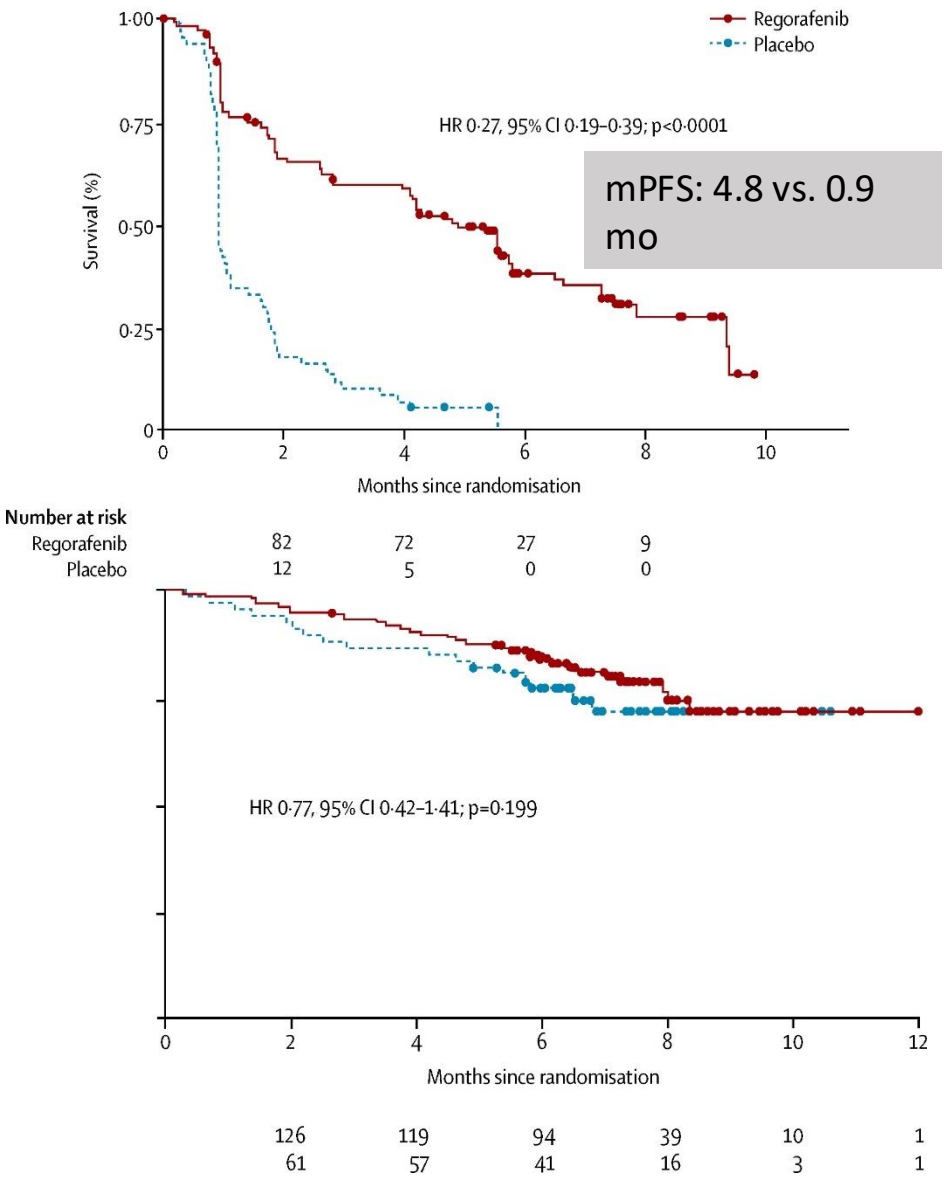
- 50mg q4/q2 or 37.5mg daily
- Second-line treatment after imatinib
- Side effects:
  - Fatigue
  - Diarrhea
  - Nausea
  - Cytopenias
  - Hypertension
  - Hand/foot syndrome
  - Mouth sensitivity

Demetri et al. Lancet. 2006;368(9544):1329

Regorafenib

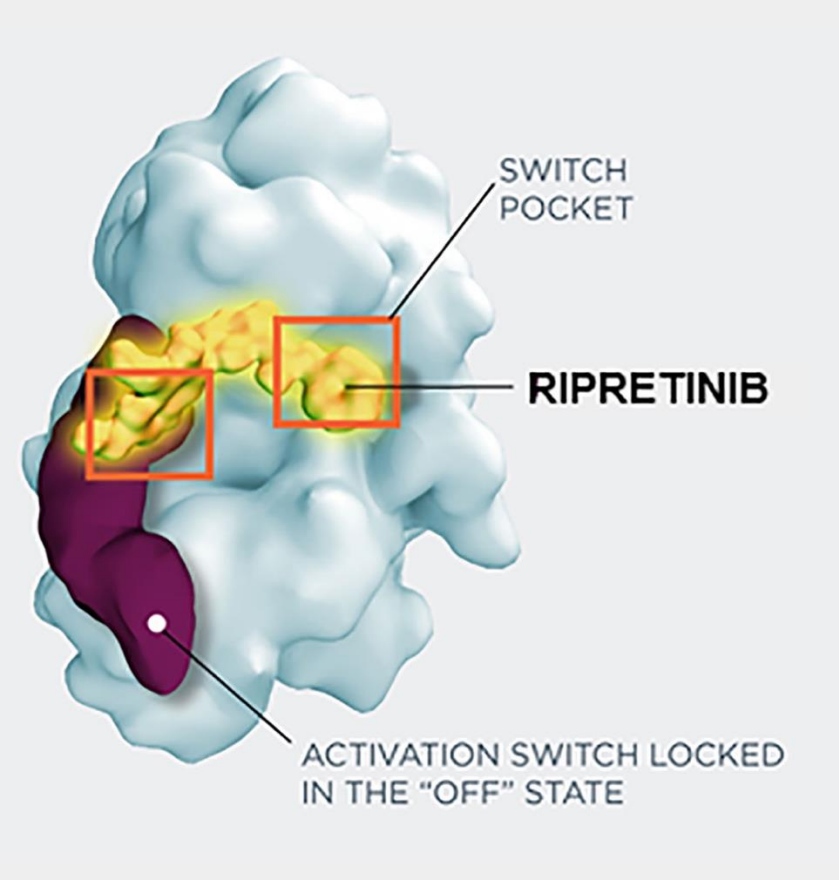


- Blocks *VEGFR1-3*, *KIT*, *RET*, *RAF1*, *BRAF*, *PDGFR*, *FGFR*
- Third-line treatment after imatinib and sunitinib
- Side effects (>20%)
  - Hand/foot rash
  - Hypertension
  - Diarrhea
  - Fatigue
  - Mouth sensitivity
  - Alopecia
  - Hoarseness
  - Anorexia



Demetri et al. Lancet. 2013;381:285-302.

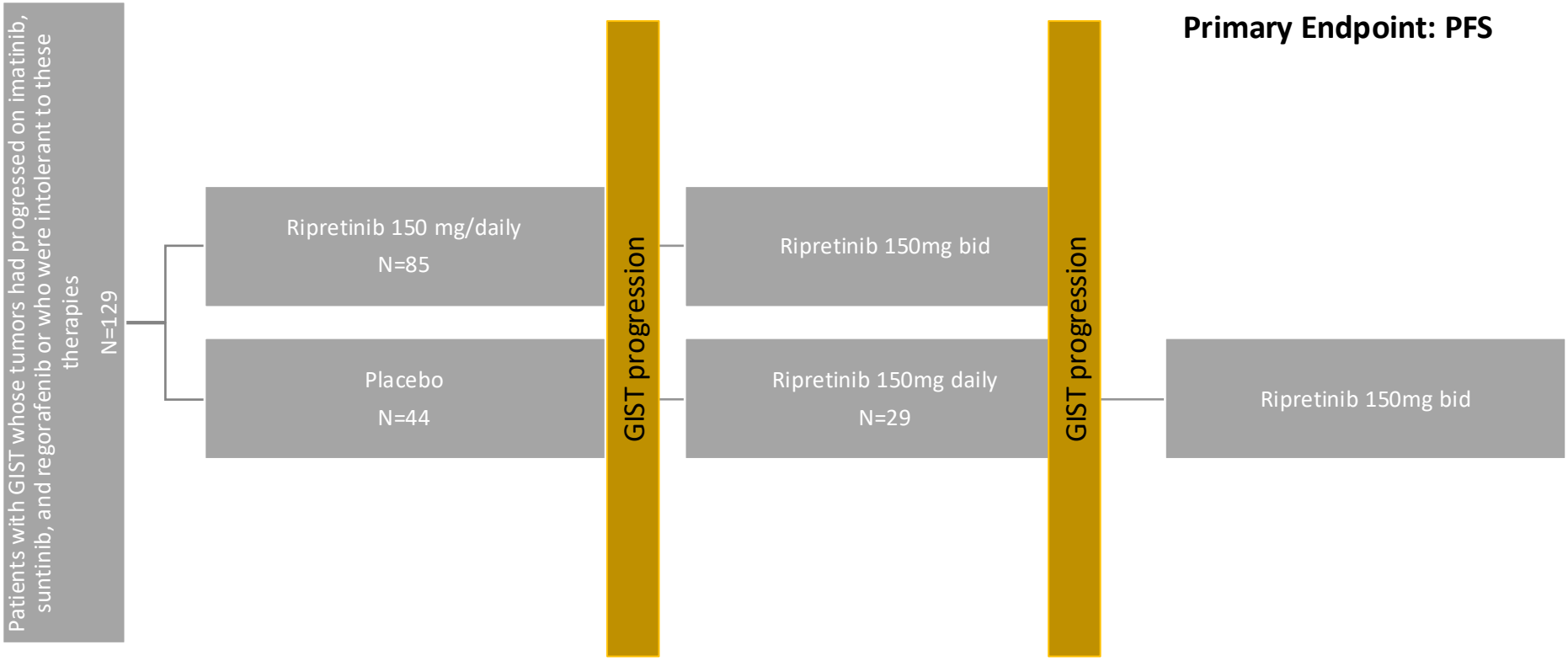
Ripretinib



- Type II switch control kinase inhibitor
- Binds to the switch pocket and the activation switch to lock the kinase in the inactive state
- Broadly inhibits *KIT* and *PDGFRA* kinase signaling
- Approved for advanced GIST treated with 3+ kinase inhibitors, including imatinib

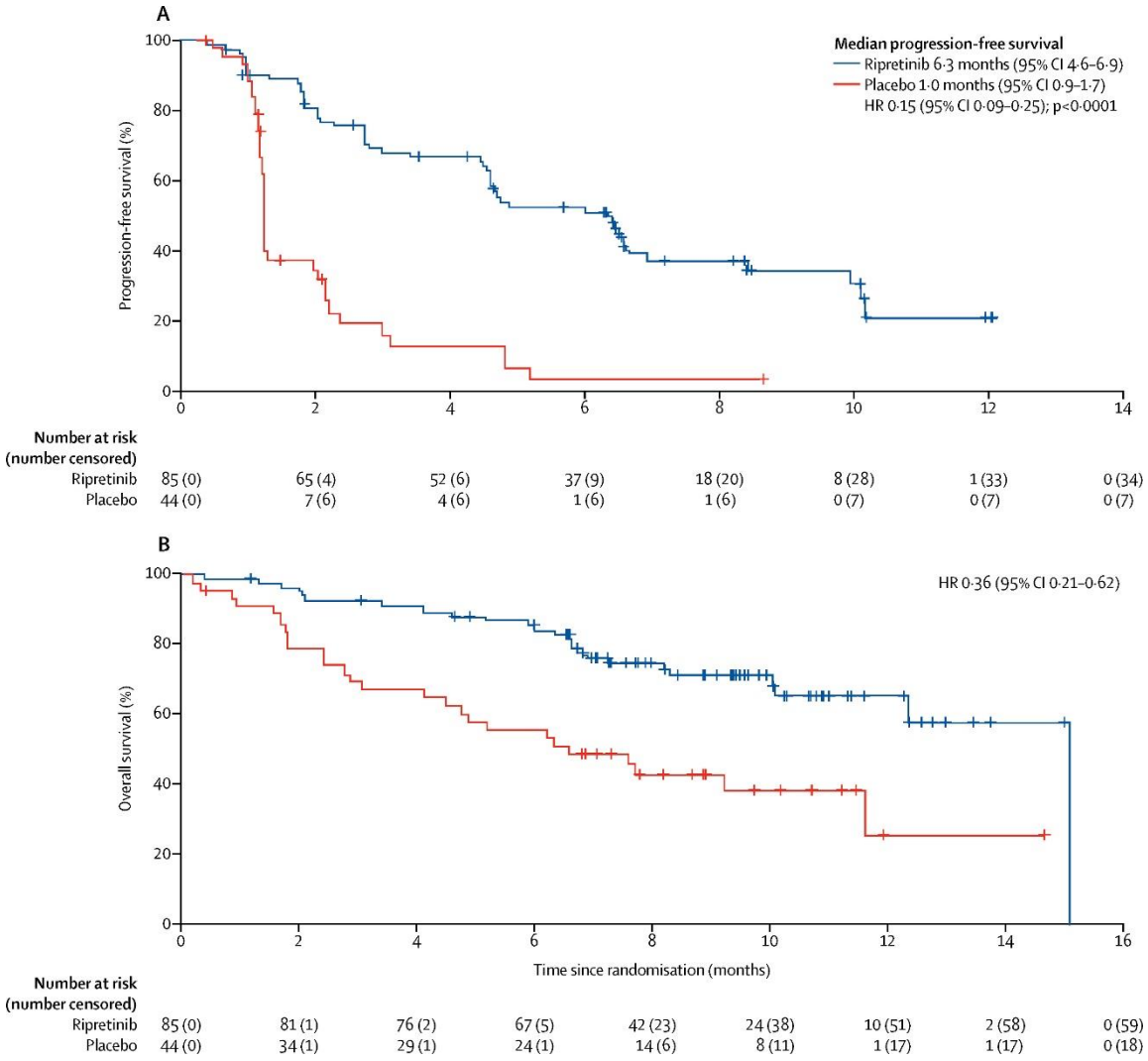
S. Bauer et al. Front. Oncol 12 July 2021.

INVICTUS schema



JY Blay et al. Lancet Oncol. 2020 July; 21 (7):923-34.

INVICTUS results



Med PFS: 6.3 vs. 1 mo

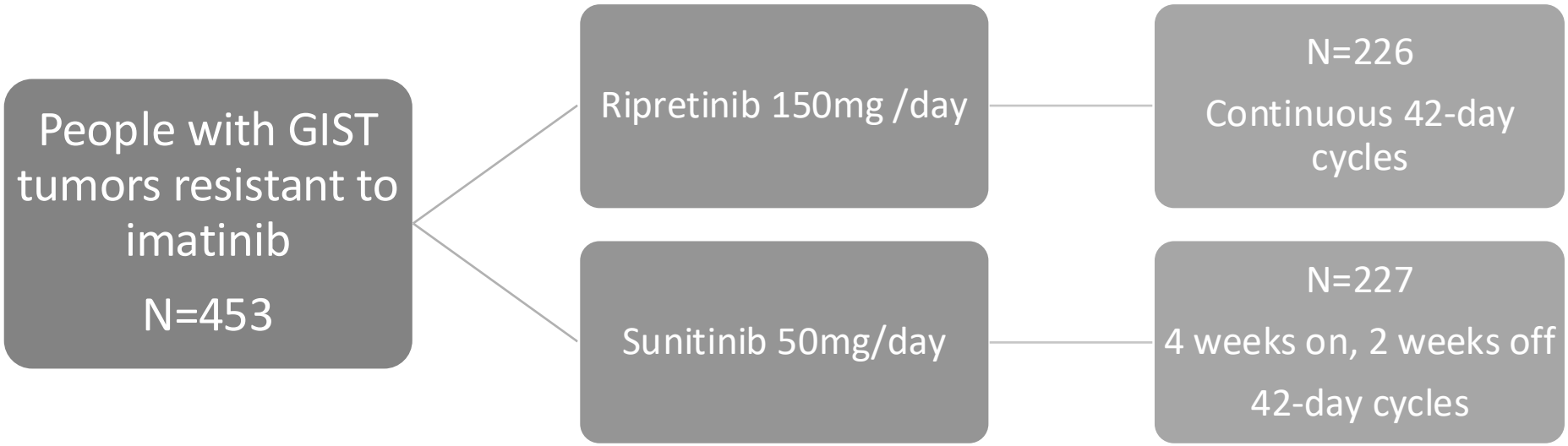
ORR: 9% vs. 0%

Median OS: 15.1 vs. 6.6 mos

INVICTUS results

- AEs (≥20%)
  - Hair loss, fatigue, nausea, abdominal pain, constipation, muscle aches, diarrhea, anorexia, hand/foot syndrome, and vomiting.
- FDA approved May 15, 2020

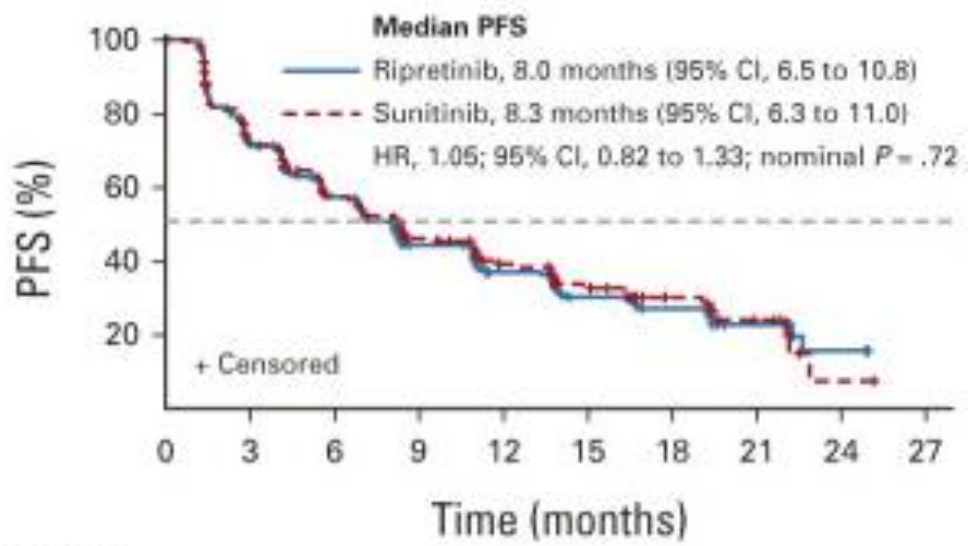
INTRIGUE study- schema



Bauer S et al. JCO. 2022 Dec 1;40(34):3918-3928.

INTRIGUE study- PFS and ORR

Progression free survival



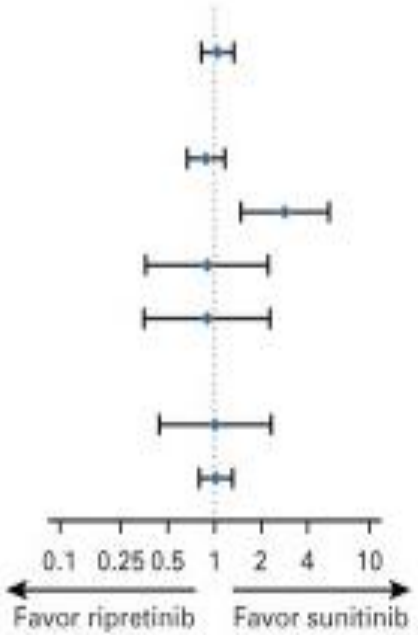
Response rates

	KIT Exon 11 ITT Population		ITT Population	
Parameter	Ripretinib (n = 163)	Sunitinib (n = 164)	Ripretinib (n = 226)	Sunitinib (n = 227)
ORR, No. (%) 95% CI	39 (23.9) 17.6 to 31.2	24 (14.6) 9.6 to 21.0	49 (21.7) 16.5 to 27.6	40 (17.6) 12.9 to 23.2
CR, No. (%)[a]	0	2 (1.2)	1 (0.4)	3 (1.3)
PR, No. (%)[b]	39 (23.9)	22 (13.4)	48 (21.2)	37 (16.3)
Difference in ORR, % (95% CI)	9.3 (0.7 to 17.8)		4.2 (−3.2 to 11.5)	
P[c]	.03		.27	
DOR, months, median (95% CI)	16.7 (12.5 to NE)	20.1 (11.0 to NE)	16.7 (12.5 to NE)	20.1 (12.3 to NE)

Bauer S et al. JCO. 2022 Dec 1;40(34):3918-3928.

INTRIGUE study- PFS subgroup analyses

	Ripretinib, No. (events)	Sunitinib, No. (events)	Median Ripretinib, months	Median Sunitinib, months	HR (95% CI)
Overall	226 (146)	227 (130)	8.0	8.3	1.05 (0.82 to 1.33)
Mutation type					
KIT exon 11	163 (100)	164 (98)	8.3	7.0	0.88 (0.67 to 1.17)
KIT exon 9	31 (27)	29 (14)	5.5	13.8	2.85 (1.48 to 5.48)
KIT/PDGFRA WT	15 (9)	18 (10)	7.0	4.1	0.90 (0.36 to 2.23)
Other *KIT/PDGFRA*	17 (10)	16 (8)	6.8	8.4	0.90 (0.35 to 2.28)
Imatinib intolerance					
Yes	22 (14)	23 (10)	13.7	10.9	1.01 (0.44 to 2.33)
No	204 (132)	204 (120)	7.1	8.1	1.02 (0.80 to 1.31)



Bauer S et al. JCO. 2022 Dec 1;40(34):3918-3928.

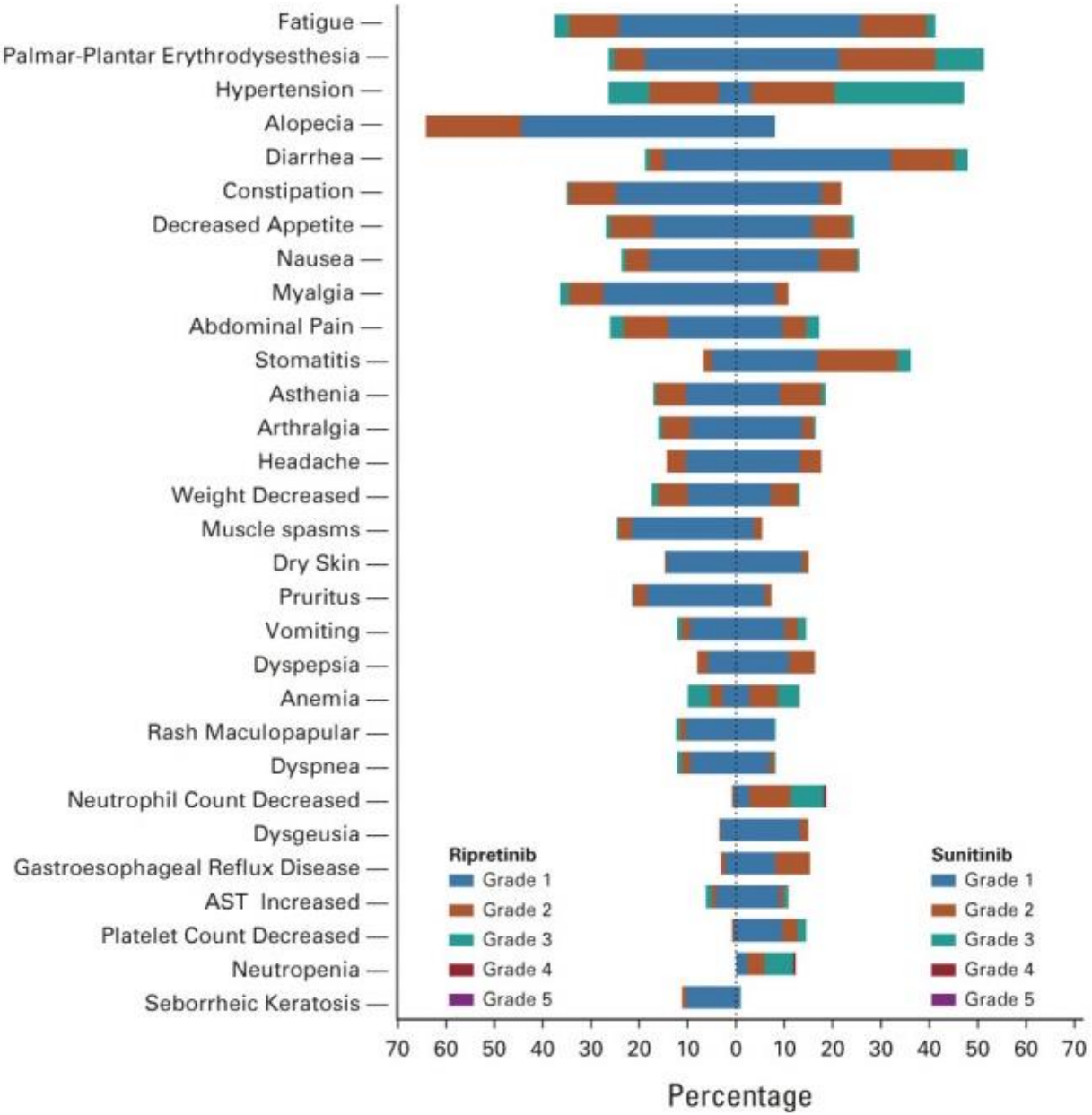
INTRIGUE study- correlative analyses

Secondary resistance mutation	Sunitinib	Ripretinib
Exon 13/14	mPFS 15 months mOS NYR	mPFS 4 months mOS 24.5 months
Exon 17/18	mPFS 1.5 months mOS 17.5 months	mPFS 14 months mOS NYR

- INSIGHT trial
  - Phase III, randomized, multicenter, open-label study
  - Ripretinib vs. sunitinib in patients with advanced GIST previously treated with imatinib harboring *KIT* exon 11 and 17/18 mutations.

Bauer S et al. JCO. 2022 Dec 1;40(34):3918-3928.

INTRIGUE study- Side effects



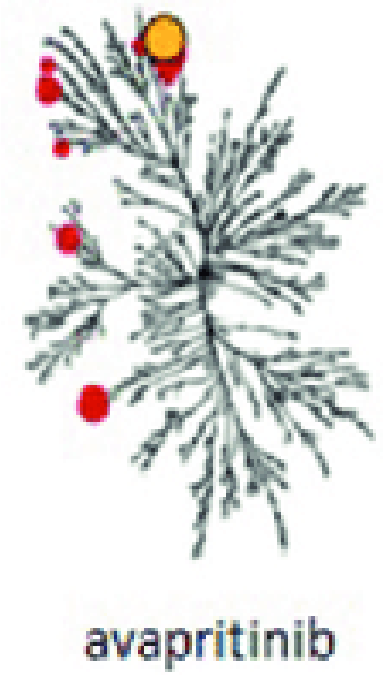
Bauer S et al. JCO. 2022 Dec 1;40(34):3918-3928.

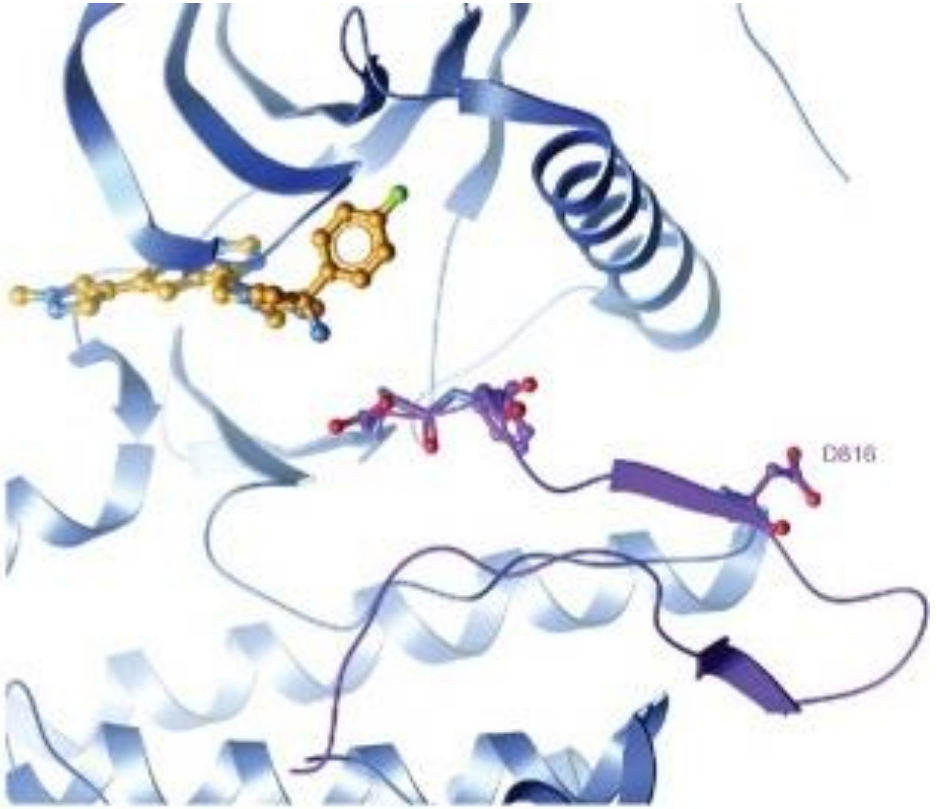
PDGFRa exon 18 D842V mutant GIST

65yo man presents with metastatic GIST with diffuse liver involvement. ECOG PS is 2. He is extremely symptomatic with anemia and pain. Mutational profiling reveals that the tumor has a PDGFRa exon 18 D842V mutation.

- ***How should this patient with untreated metastatic disease be approached?***

Avapritinib



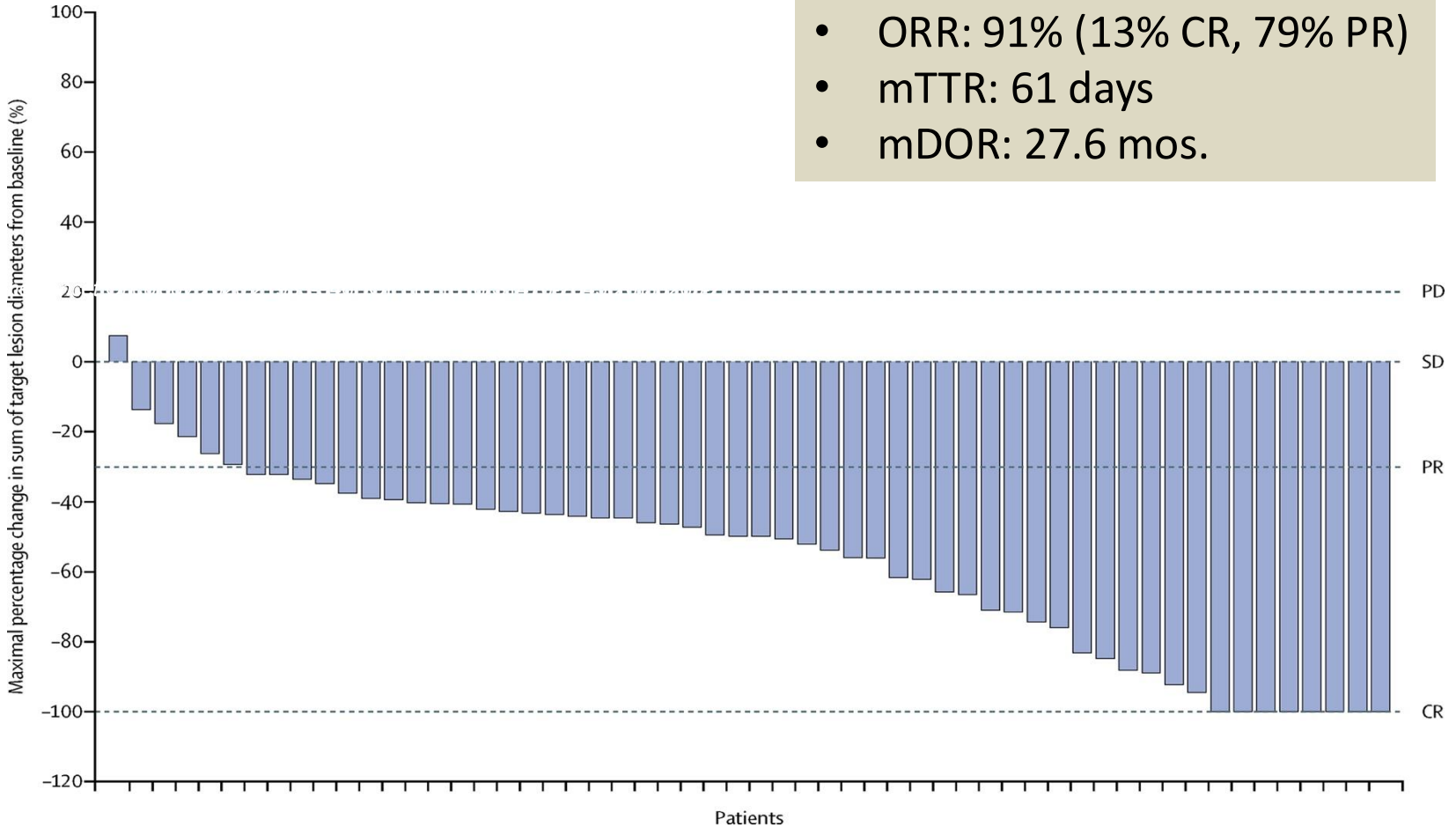


- Type 1 kinase inhibitor
- Potent and selective inhibitor of *KIT* and *PDGFRA* activation loop mutations
- Approved for treatment of GISTs with PDGFRA exon 18 mutation, including D842V mutations

Gardino et al. Mol Cell Oncol. 2018 Apr 11.

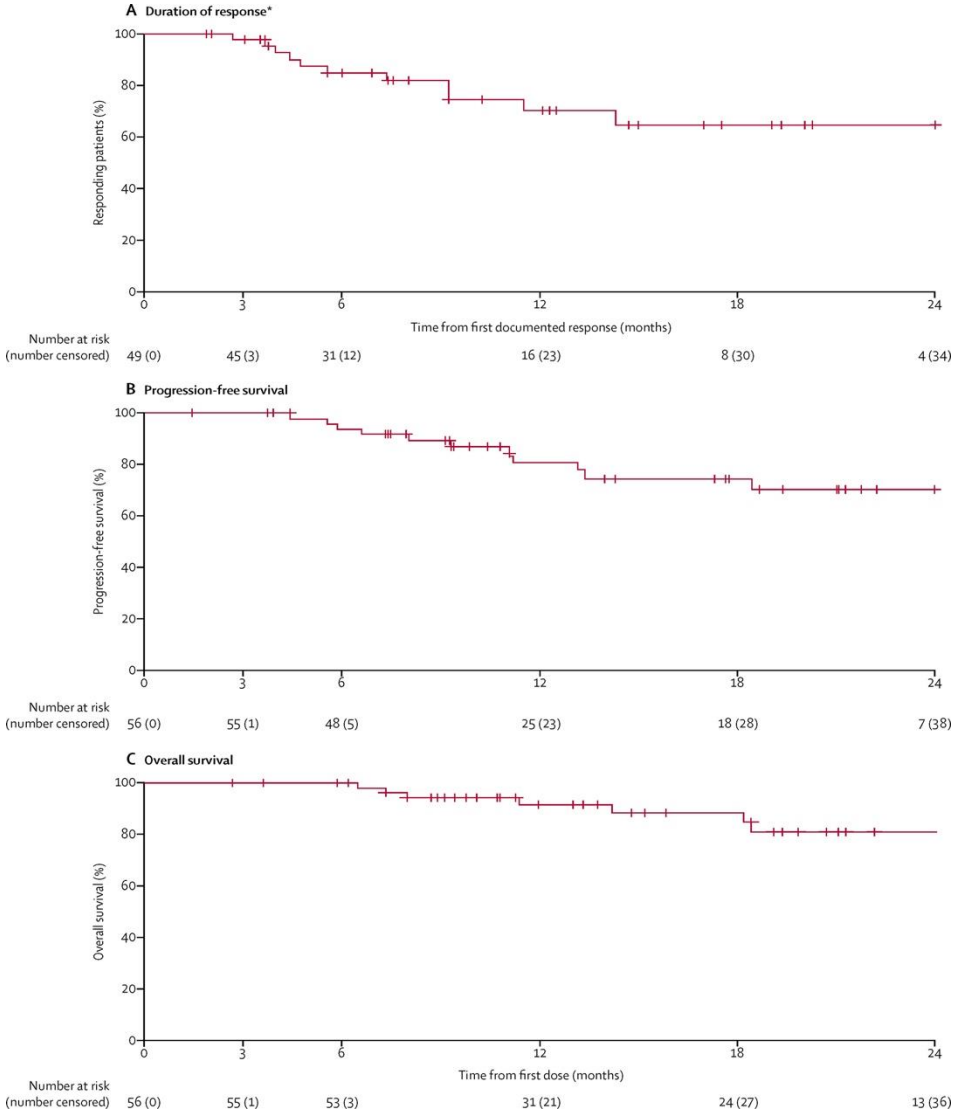
NAVIGATOR study

- PDGFRa D842V mutant GIST (n=56)
- ORR: 91% (13% CR, 79% PR)
- mTTR: 61 days
- mDOR: 27.6 mos.



The Lancet Oncology 2020 21935-946DOI: (10.1016/S1470-2045(20)30269-2)

NAVIGATOR study



12 mo. DOR- 71%

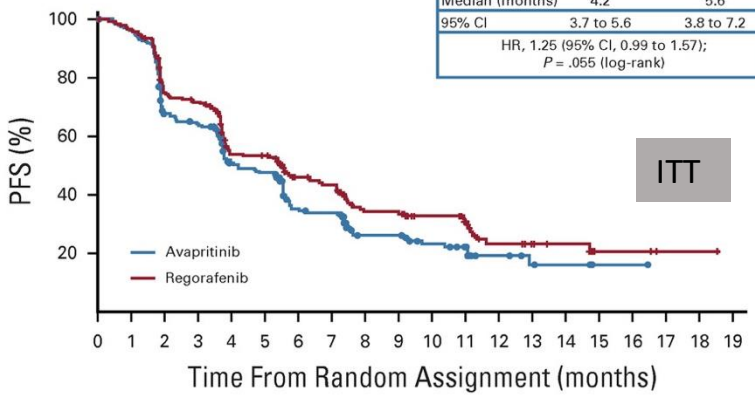
12 mo. PFS= 81%

12 mo. OS= 91%

The Lancet Oncology 2020 21935-946DOI: (10.1016/S1470-2045(20)30269-2)

VOYAGER study

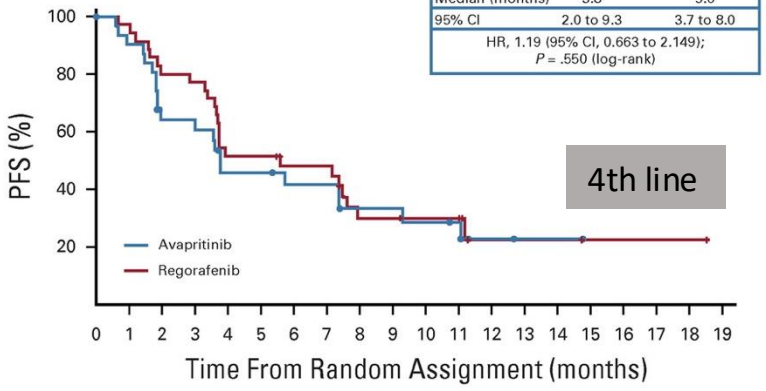
	Avapritinib (n = 240)	Regorafenib (n = 236)
Events, No.	154	145
Median (months)	4.2	5.6
95% CI	3.7 to 5.6	3.8 to 7.2
HR, 1.25 (95% CI, 0.99 to 1.57); $P = .055$ (log-rank)		



ITT

No. at risk:																		
Avapritinib	240	221	151	142	94	88	53	50	29	29	22	17	8	5	4	1	1	0
Regorafenib	236	224	169	161	108	106	71	66	46	46	36	31	15	11	9	3	3	1	1	0

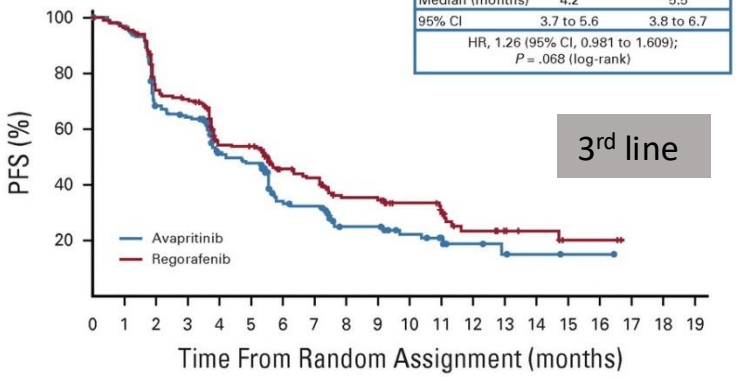
	Avapritinib (n = 33)	Regorafenib (n = 35)
Events, No.	21	24
Median (months)	3.8	5.6
95% CI	2.0 to 9.3	3.7 to 8.0
HR, 1.19 (95% CI, 0.663 to 2.149); $P = .550$ (log-rank)		



4th line

No. at risk:																			
Avapritinib	33	28	18	18	12	12	10	10	7	7	6	5	2	1	1	0			
Regorafenib	35	34	28	27	18	18	14	14	8	8	7	7	2	2	2	1	1	1	1	0

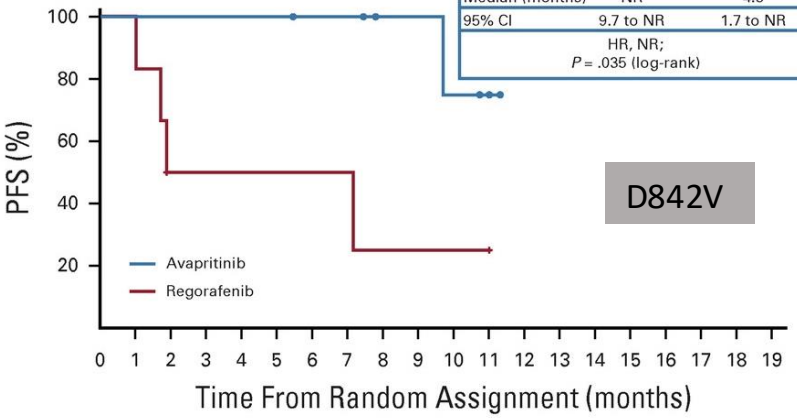
	Avapritinib (n = 207)	Regorafenib (n = 201)
Events, No.	133	121
Median (months)	4.2	5.5
95% CI	3.7 to 5.6	3.8 to 6.7
HR, 1.26 (95% CI, 0.981 to 1.609); $P = .068$ (log-rank)		



3rd line

No. at risk:																	
Avapritinib	207	193	133	124	82	76	43	40	22	22	16	12	6	4	3	1	1	0
Regorafenib	201	190	141	134	90	88	57	52	38	38	29	24	13	9	7	2	2	0

	Avapritinib (n = 7)	Regorafenib (n = 6)
Events, No.	1	4
Median (months)	NR	4.5
95% CI	9.7 to NR	1.7 to NR
HR, NR; $P = .035$ (log-rank)		



D842V

No. at risk:														
Avapritinib	7	7	7	7	7	7	6	6	4	4	3	2	0	
Regorafenib	6	6	2	2	2	2	2	2	1	1	1	1	0	

Kang YK et al. JCO 2021.28:3128-39.

Treatment for metastatic GIST

- 1st-line
  non-PDGFRa exon 18 mutant GIST
  - Imatinib 400mg daily

  PDGFRa exon 18 mutant GIST
  - Avapritinib 300mg daily
  - Clinical trial
- 2nd-line
  - Sunitinib 37.5mg daily *OR* 50mg daily 4 weeks on/2 weeks off
  - Clinical trial
- 3rd-line
  - Regorafenib 160mg daily 3 weeks on/1 week off
  - Clinical trial
- 4th-line
  - Ripretinib 150mg daily
  - Clinical trial
- 5th-line +
  - Other TKIs (off-label), imatinib re-challenge

GIST "Top ten" list

1. GIST strikes randomly – getting GIST is not your fault.

2. GISTs are rare! Find a GIST specialist.

3. Ask whether your GIST is 'localized' or has 'metastasized'.

4. Review your pathology report with your doctor.

5. Ask whether mutational testing of the GIST should be performed.

6. Five oral drugs (TKIs) are approved for GIST.

7. Unlike the common GI tract cancers, GISTs respond best to TKIs not chemo.

8. For localized GIST, adjuvant imatinib can reduce the risk of recurrence.

9. Side effects of GIST drugs should be discussed with your doctor.

10. Reach out! Join a support group such as Life Raft Group.

Questions?

Thank you to our sponsors for supporting our mission to present high-quality education, engagement & support to the GIST community!

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