Treatment Paradigms for Primary and Resistant Gastrointestinal Stromal Tumor (GIST)

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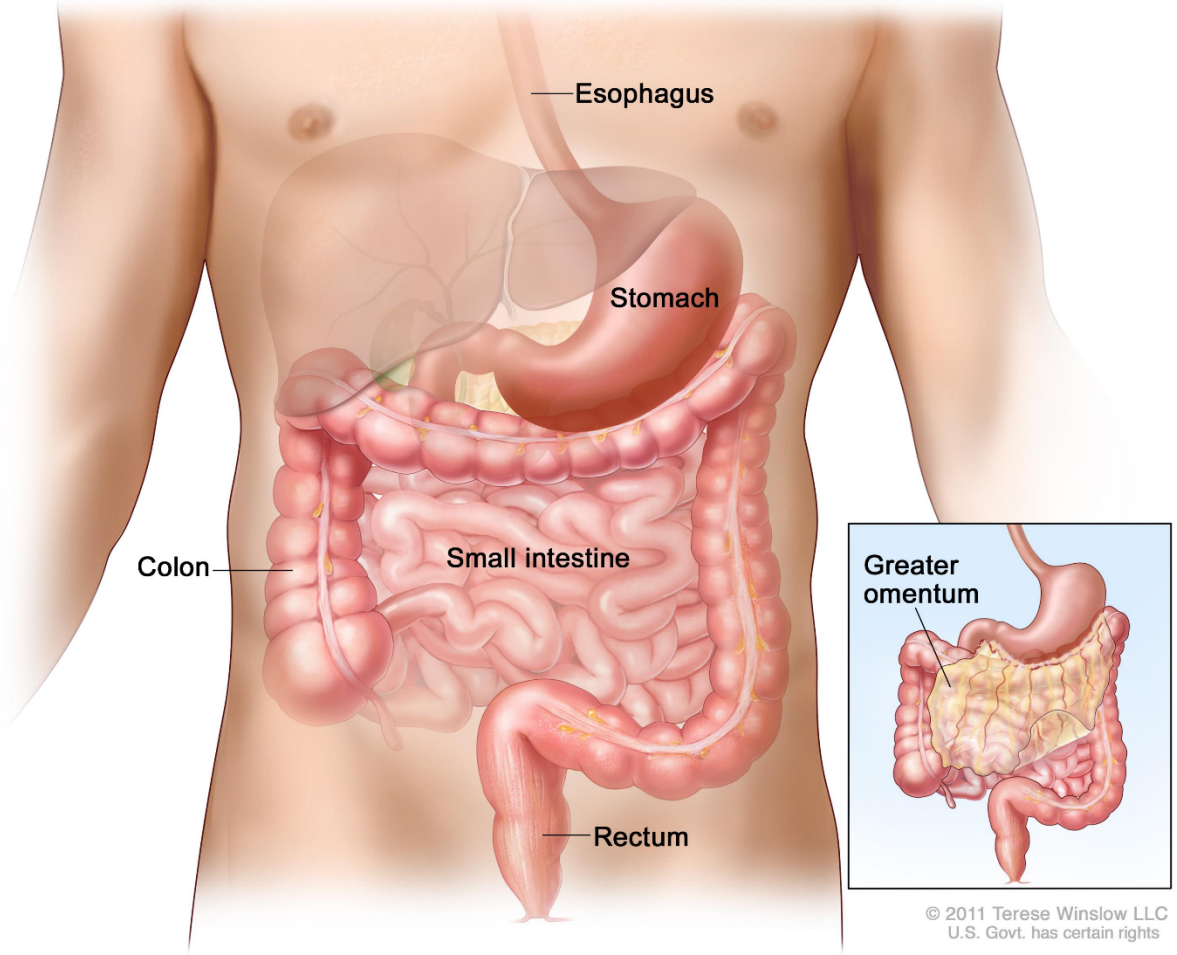
DISCLOSURES

- Speaker's Bureau: Eli Lilly, Eisai
- Advisory Role: Eli Lilly
- Founder: PDOX LLC.

WHERE DOES GIST START?



- Stomach (60%).
- Small intestine (30%).
- Rectum (3%).
- Colon (1–2%).
- Esophagus (<1%).
- Omentum/mesentery (rare).

Treatment planning

Must haves

Multidisciplinary team
Medical history and physical exam
Biopsy if • <2 cm stomach tumor, • ≥2 cm GI tumor and may have other types of treatment before surgery, or • ≥2 cm GI tumor and can't have surgery but will have other treatment
Imaging of abdomen and pelvis • CT (**c**omputed **t**omography) for <2 cm stomach tumors • CT or MRI (**m**agnetic **r**esonance **i**maging) for ≥2 cm tumor
KIT and PDGFRA testing for ≥2 cm tumor

Sometimes useful

Imaging of chest
Endoscopy ± ultrasound
PET (**p**ositron **e**mission **t**omography)
SDH (**s**uccinate **de**hydrogenase) gene testing

David Geffen School of Medicine

UCLA Health

GIST CATEGORIES

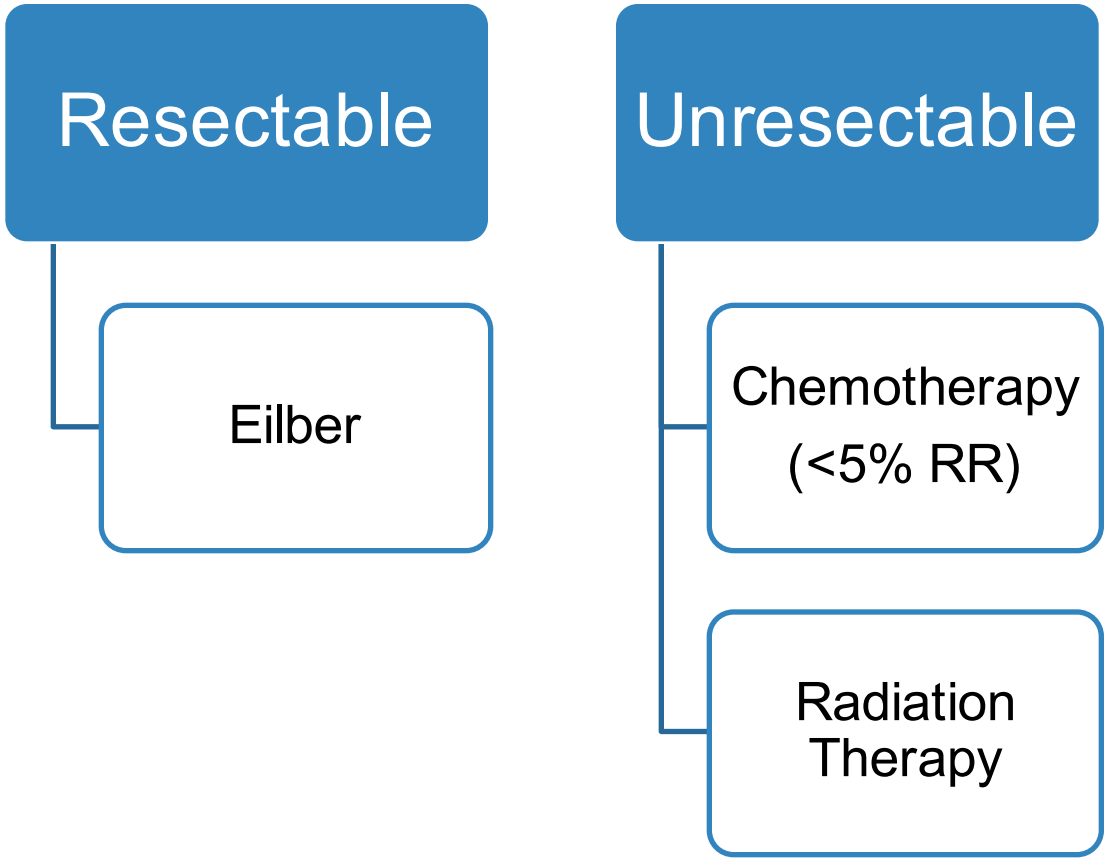
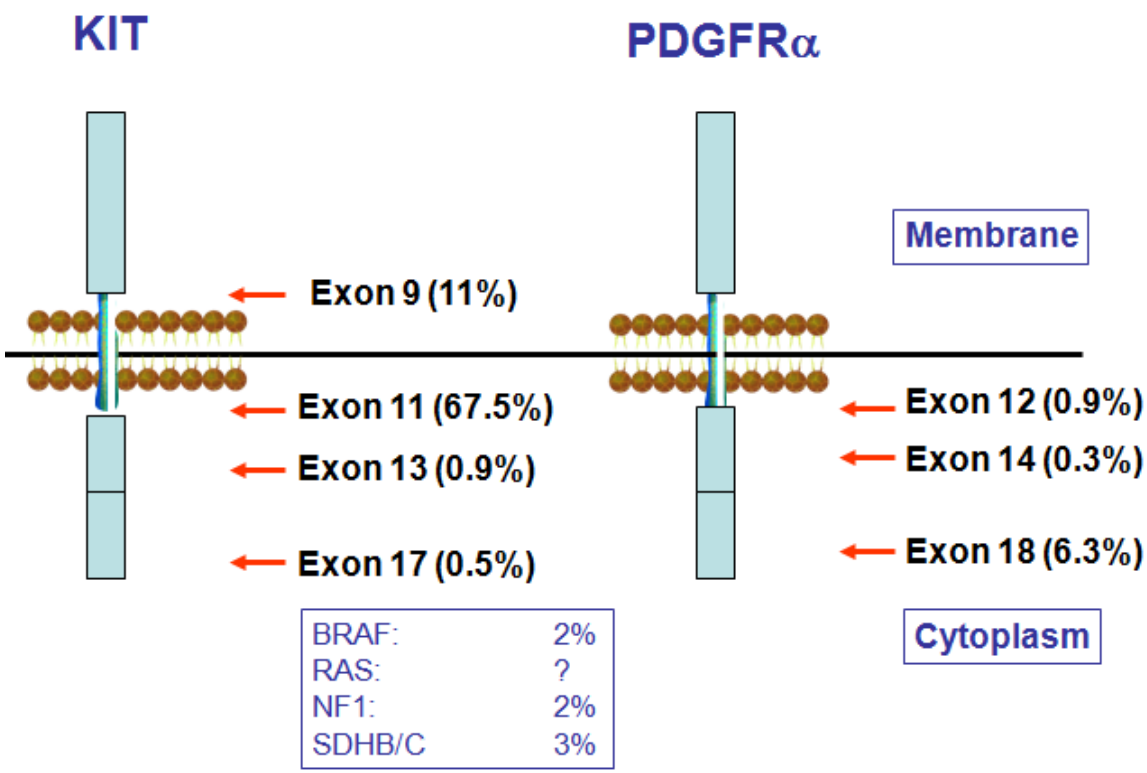


Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)

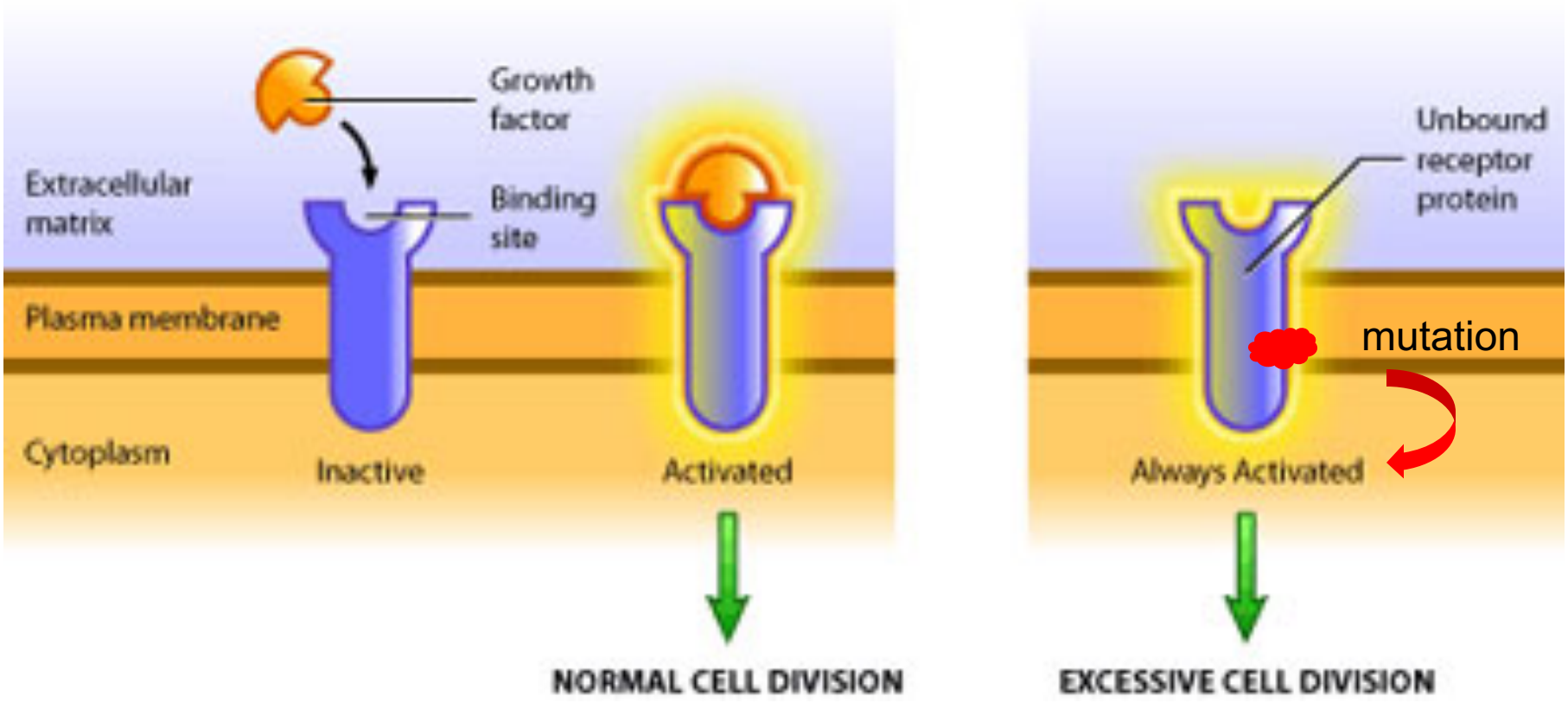
Tumor Parameters		Risk of Progressive Disease# (%)			
Mitotic Rate	*Size*	*Gastric*	*Duodenum*	*Jejunum/Ileum*	*Rectum*
≤5 per 50 high-power fields (HPF)	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 50 HPF	≤2 cm	None##	(Insufficient data)	High##	High (54%)
	>2 - ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

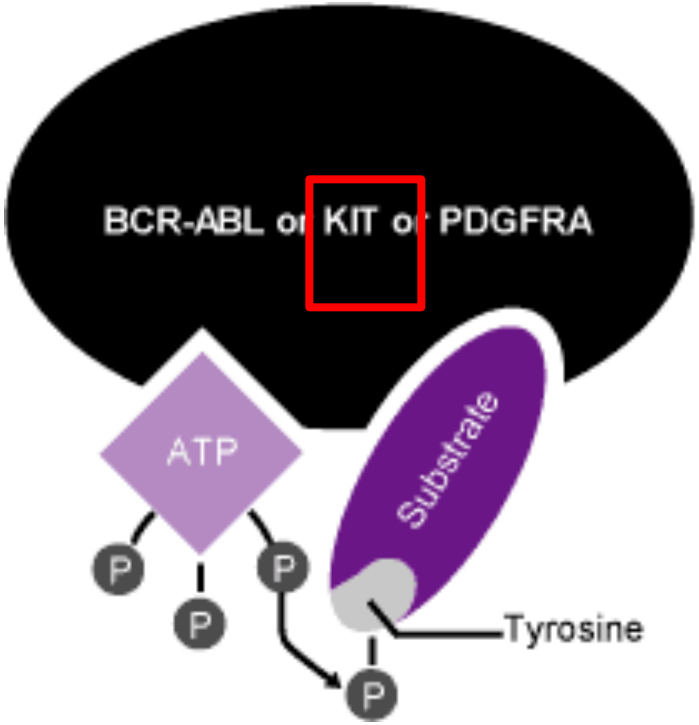
Defined as metastasis or tumor-related death.
Denotes small number of cases.

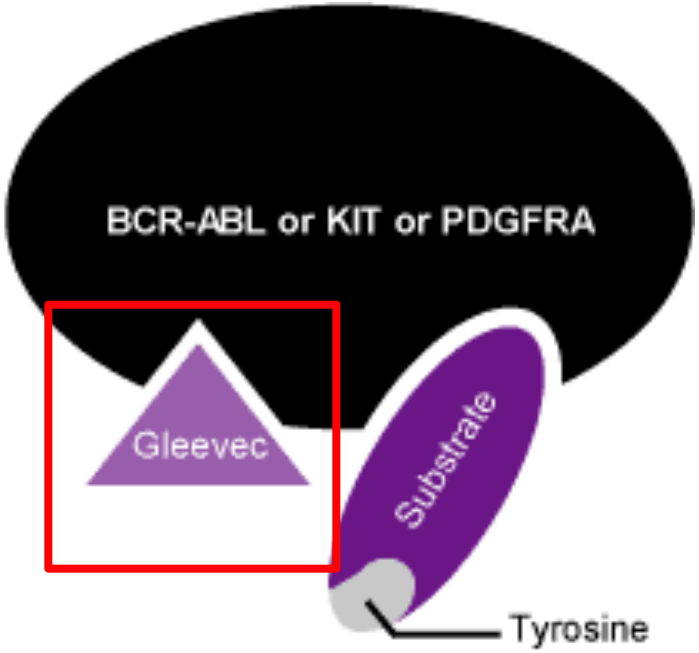
GIST MUTATIONS



WHAT DOES IT MEAN TO HAVE A MUTATION?




BCR-ABL or KIT or PDGFRA
ATP
P
P
P
P
Substrate
Tyrosine


BCR-ABL or KIT or PDGFRA
Gleevec
Substrate
Tyrosine

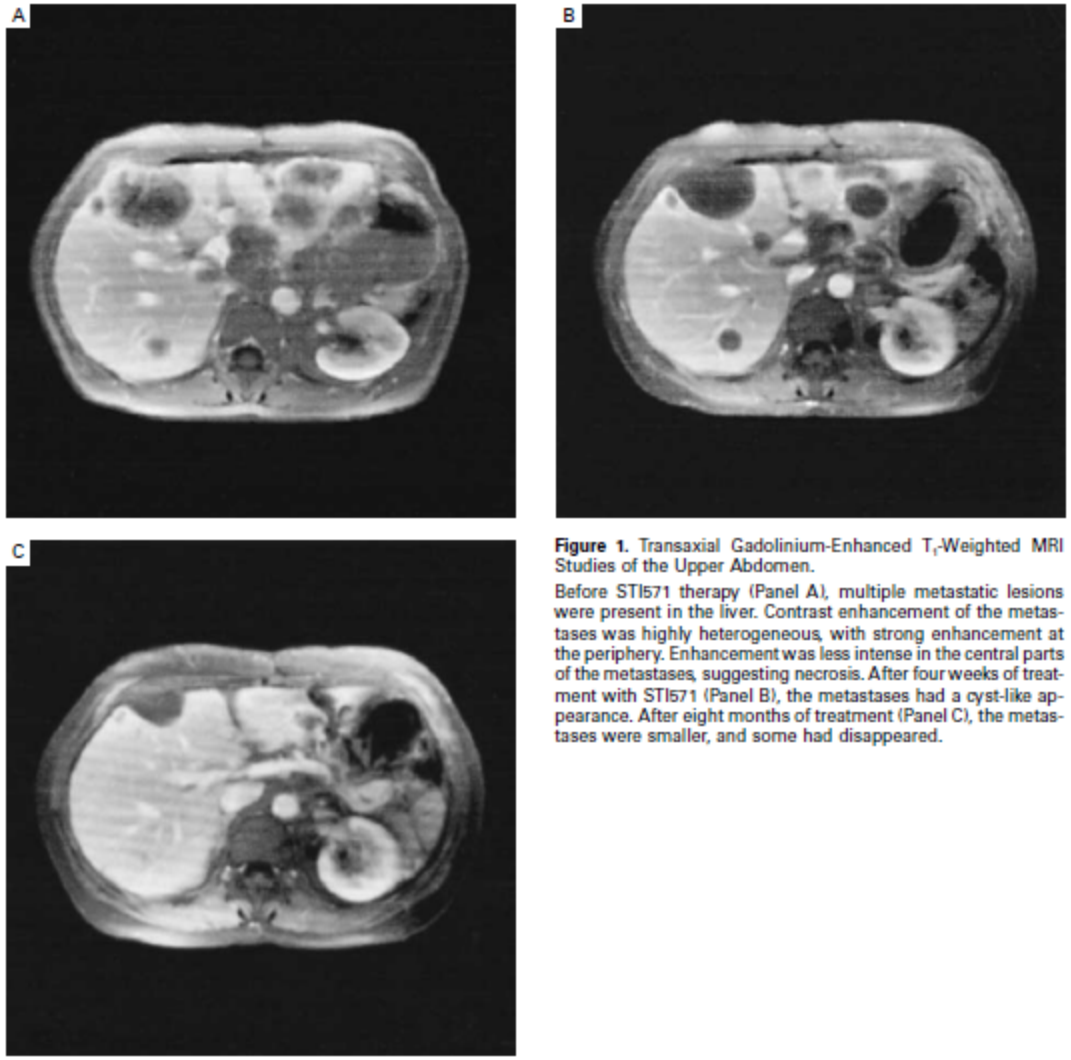


Figure 1. Transaxial Gadolinium-Enhanced T_1-Weighted MRI Studies of the Upper Abdomen.

Before STI571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with STI571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.

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.

The New England Journal of Medicine

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.

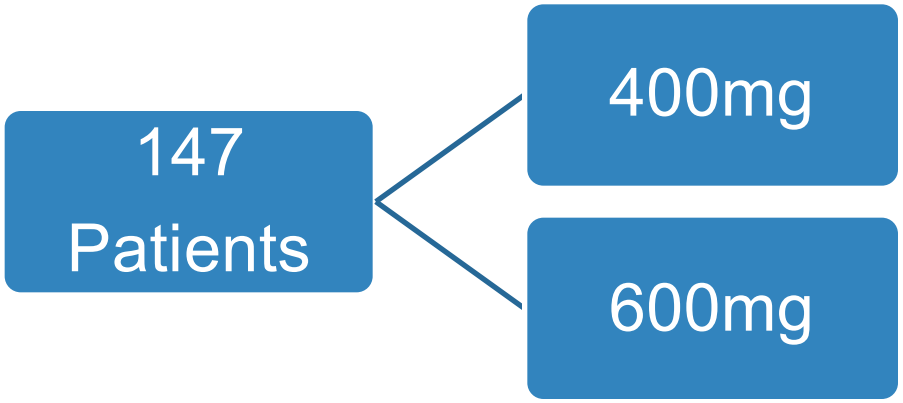


Table 2. Responses to Imatinib in Patients with Advanced Gastrointestinal Stromal Tumors.*

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)

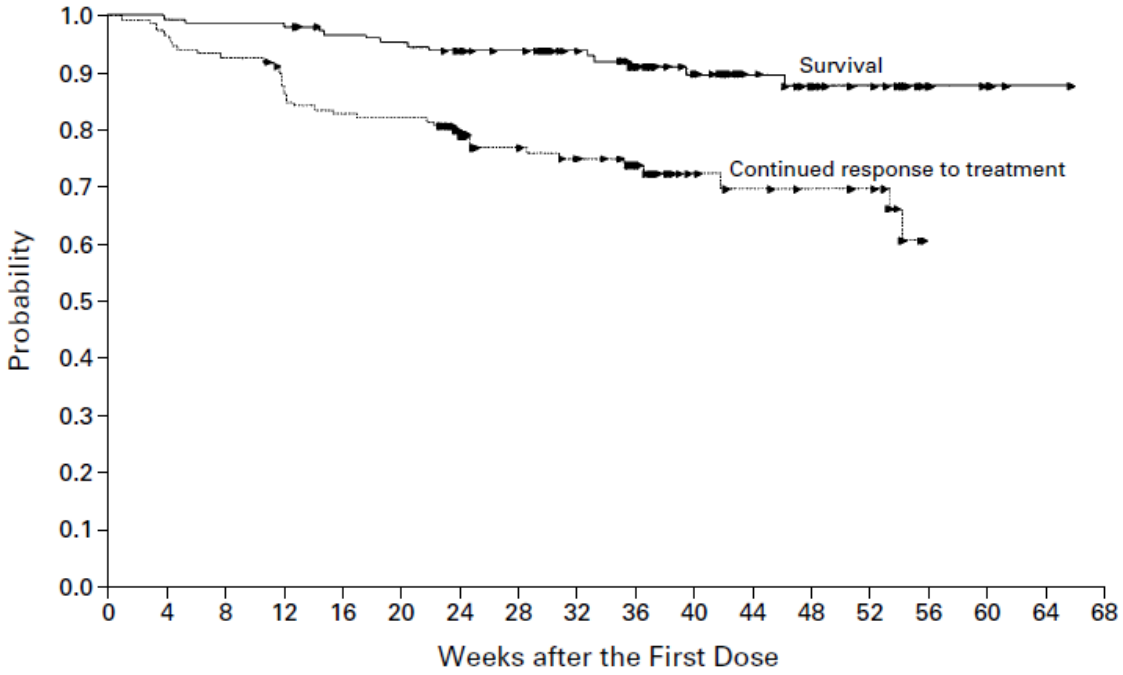
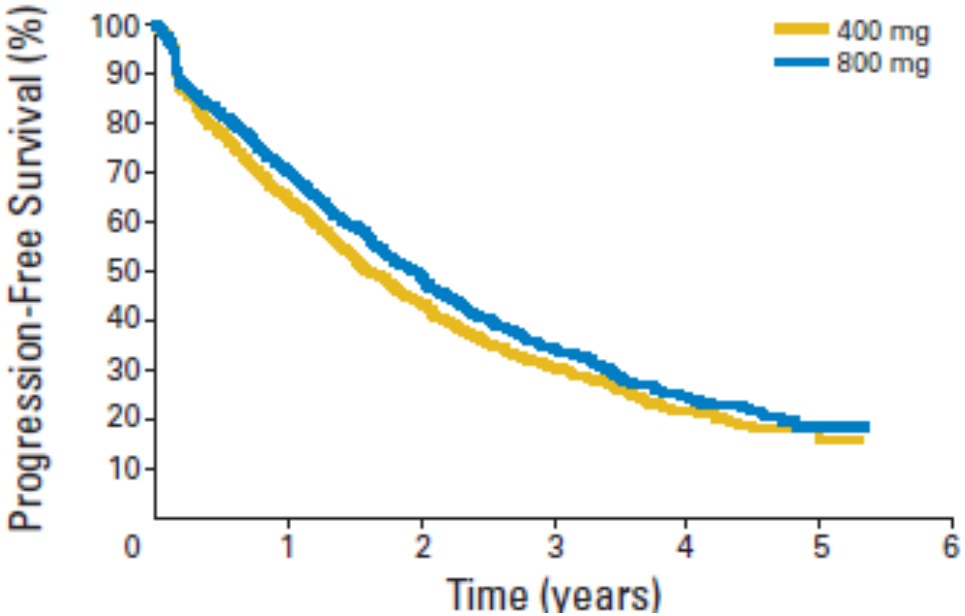


Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.

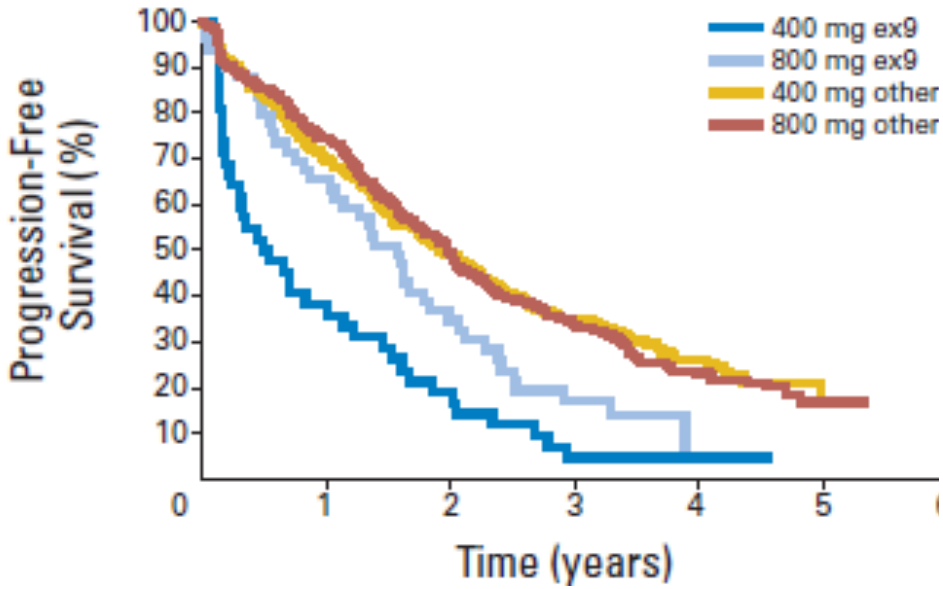
What is the right dose of Gleevec?

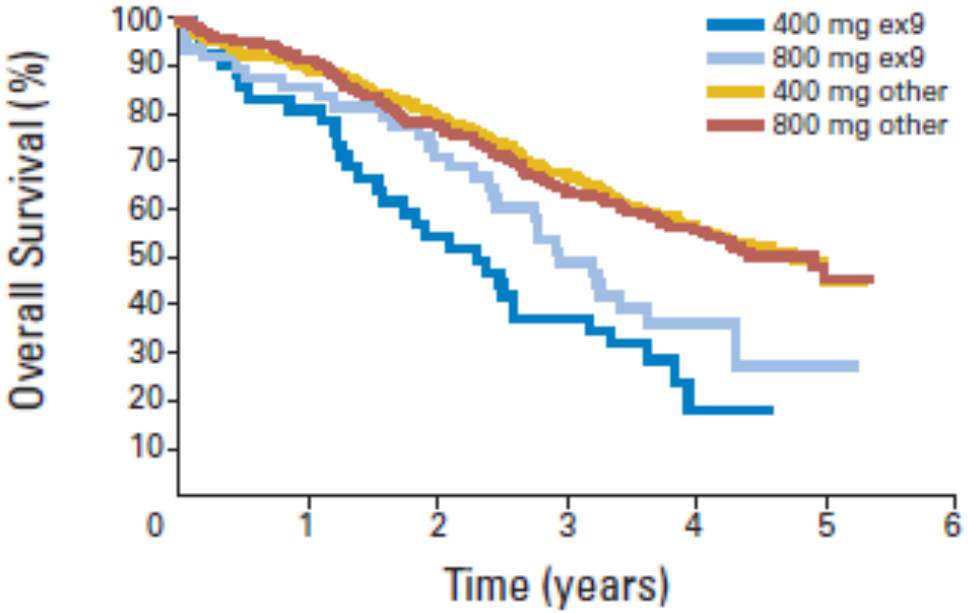


- 1640 pts with advanced GIST

J Clin Oncol 28:1247-1253.

Response by Mutational Status





J Clin Oncol 28:1247-1253.

Response by Genotype

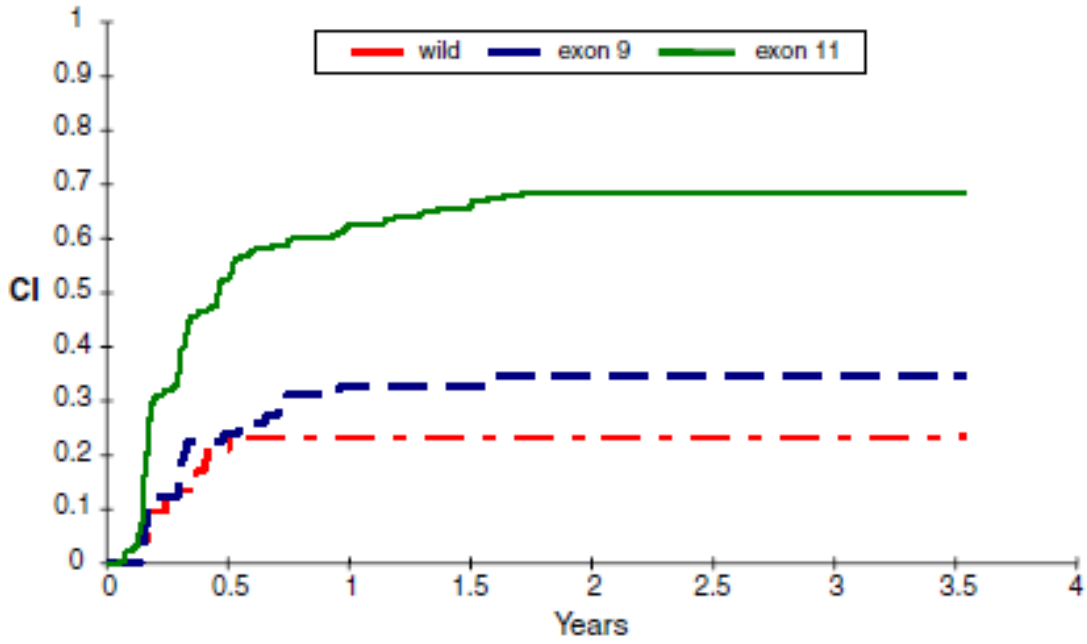
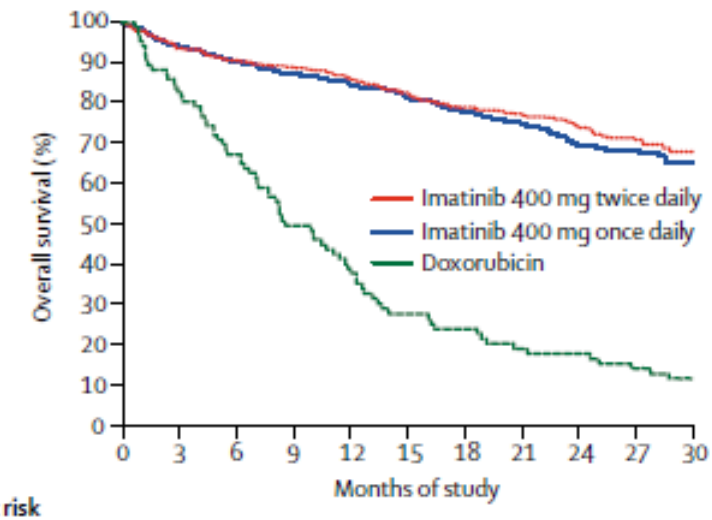


Fig. 3 – Cumulative incidence of response observed in the three largest subgroups of kinase genotypes analyzed in this study.

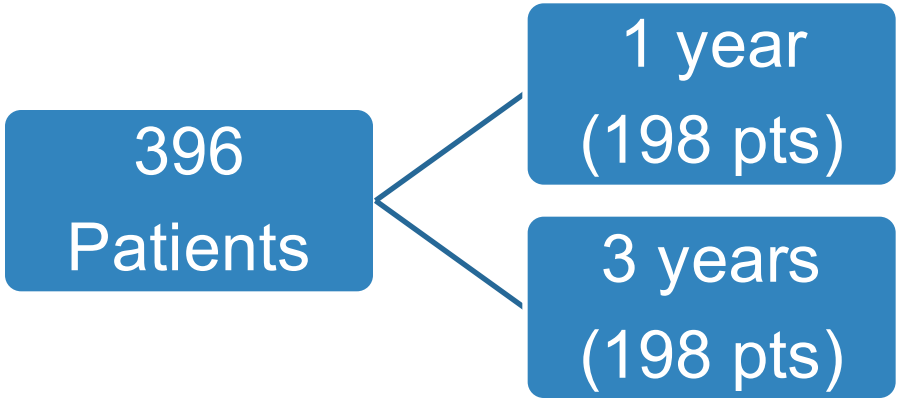
How does Gleevec compare to Chemotherapy?



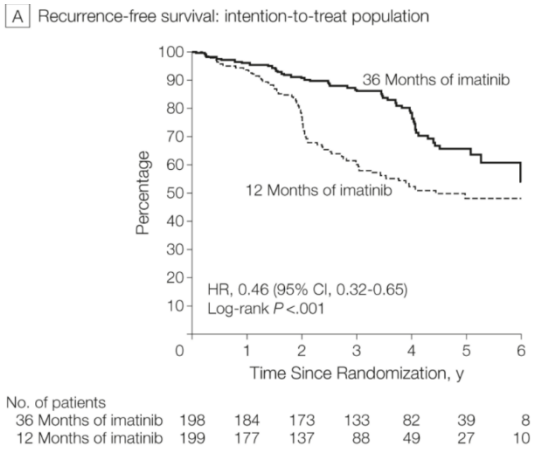
Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Figure 6: **Overall survival for total study population**
Data are compared with historical (GIST) controls from the EORTC database.
Dox=doxorubicin-based regimen

Adjuvant Treatment = After Surgery
How Long?



JAMA. 2012;307(12):1265-1272.



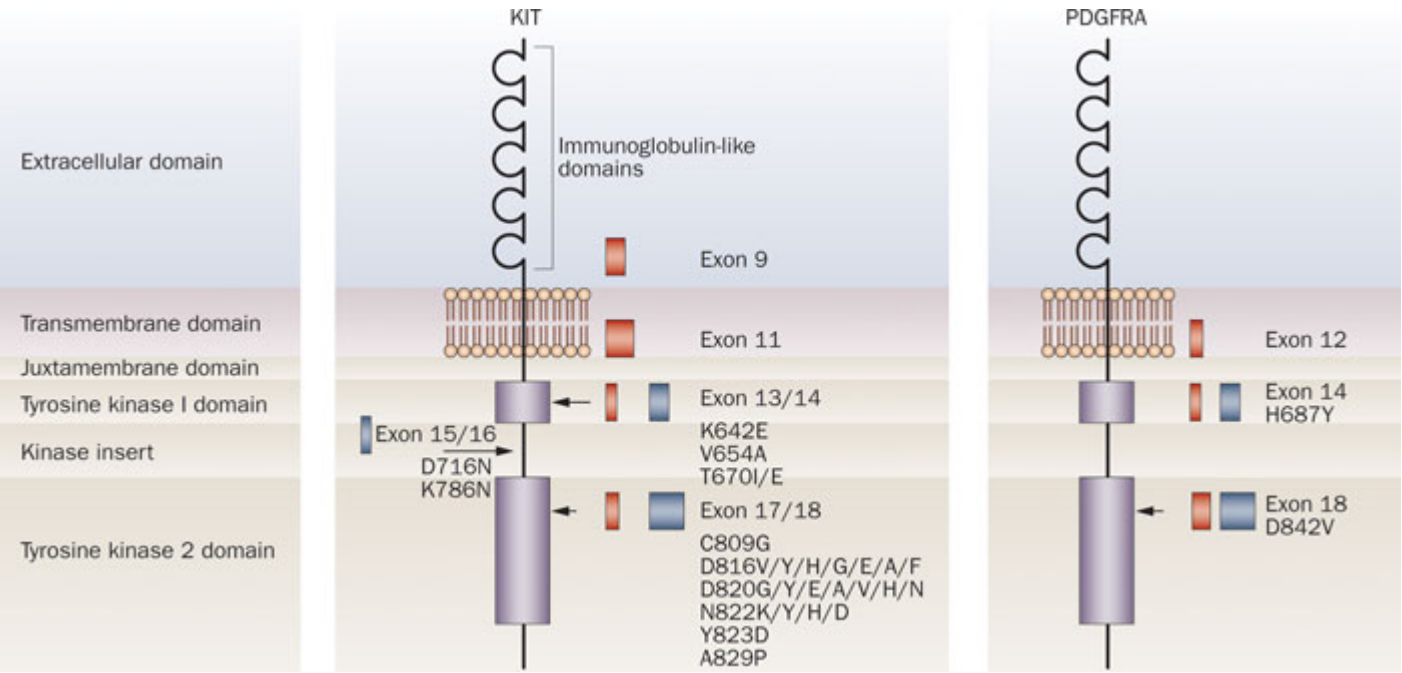
- 2/1/2012
- FDA Grants Expanded Approval of Gleevec for 36 months in adjuvant setting

JAMA. 2012;307(12):1265-1272

Resistance to Imatinib

- 5% primary resistance
- 14% have early resistance
- Secondary /acquired resistance
  - Median of 2 years

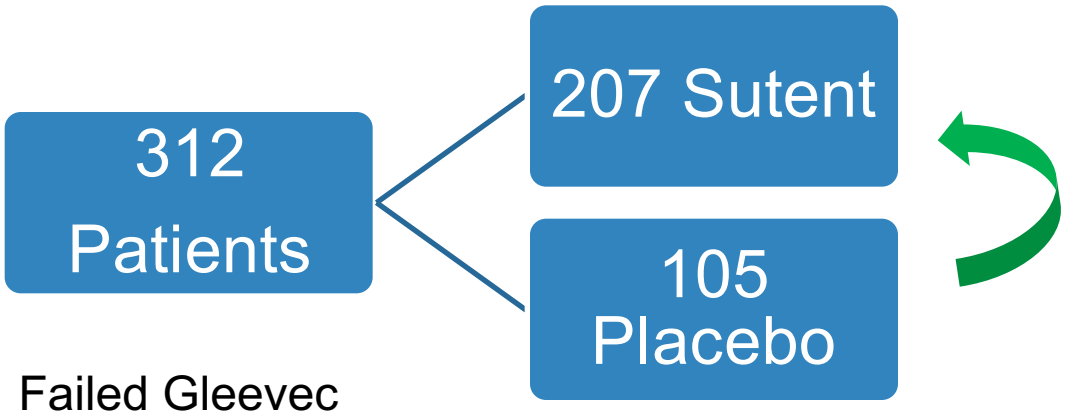
KIT and *PDGFRA* mutations and correlation to protein structure



Pierotti, M. A. *et al.* (2011) Targeted therapy in GIST: *in silico* modeling for prediction of resistance
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2011.3

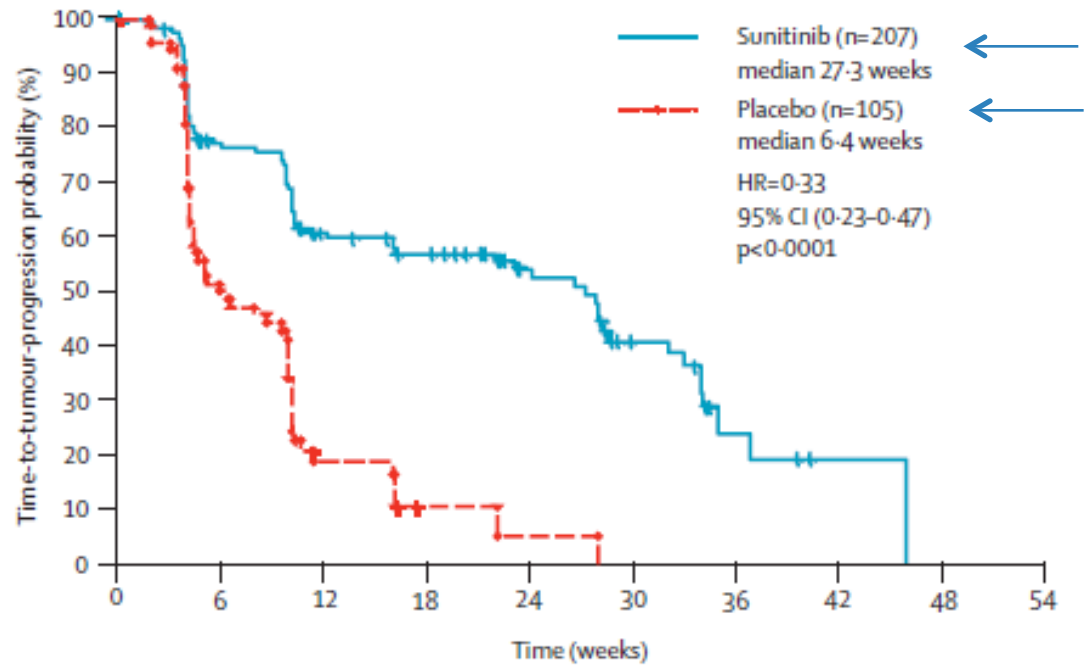
Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali



- Failed Gleevec
- Intolerant of Gleevec

Response to Sutent



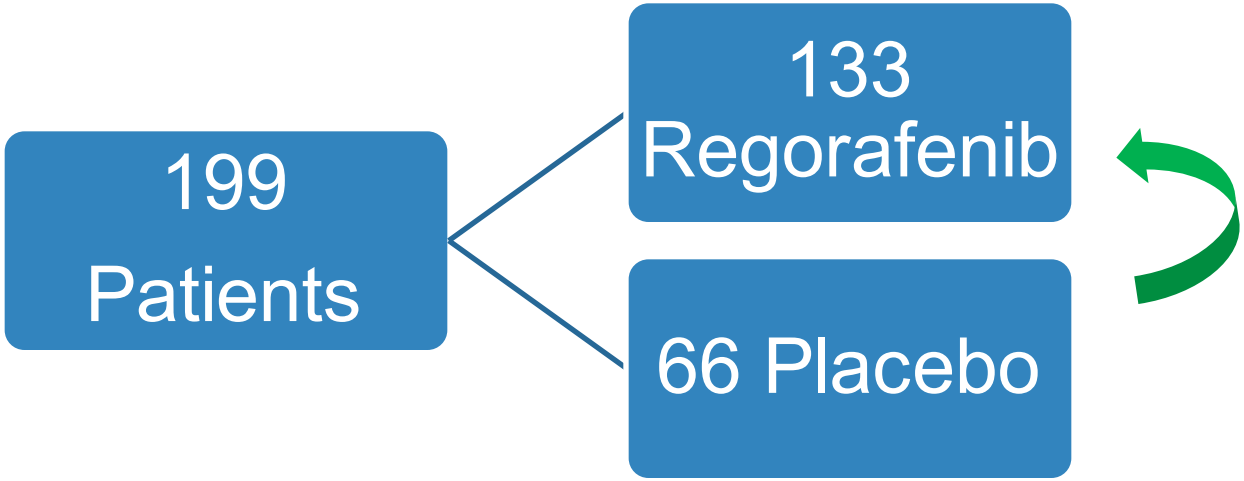
Number at risk

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

Response to Sutent

Response	Sutent	Placebo
Partial Response	7%	0%
Stable	58%	48%
Progressed	19%	37%

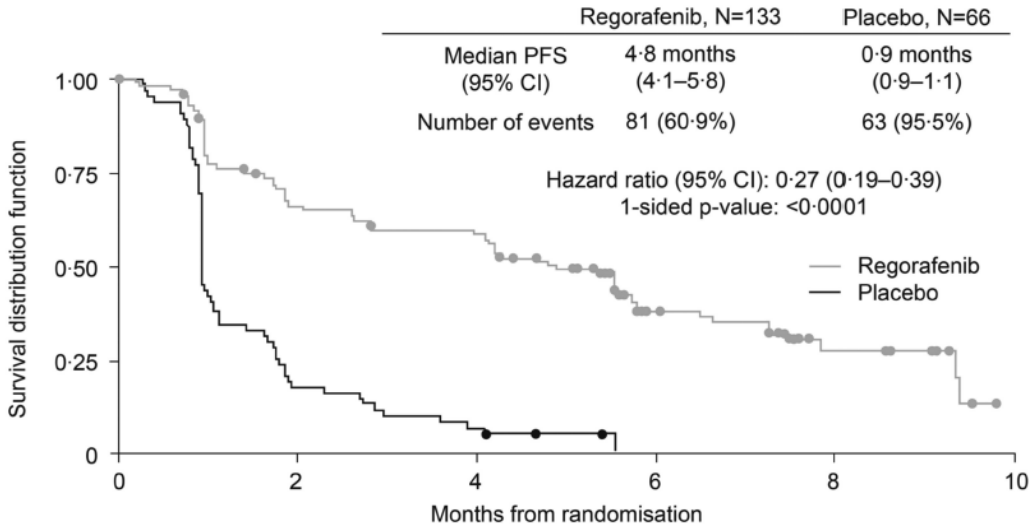
After Failing Gleevec, Sutent



Lancet. 2013 January 26; 381(9863): . doi:10.1016/S0140-6736(12)61857-1.

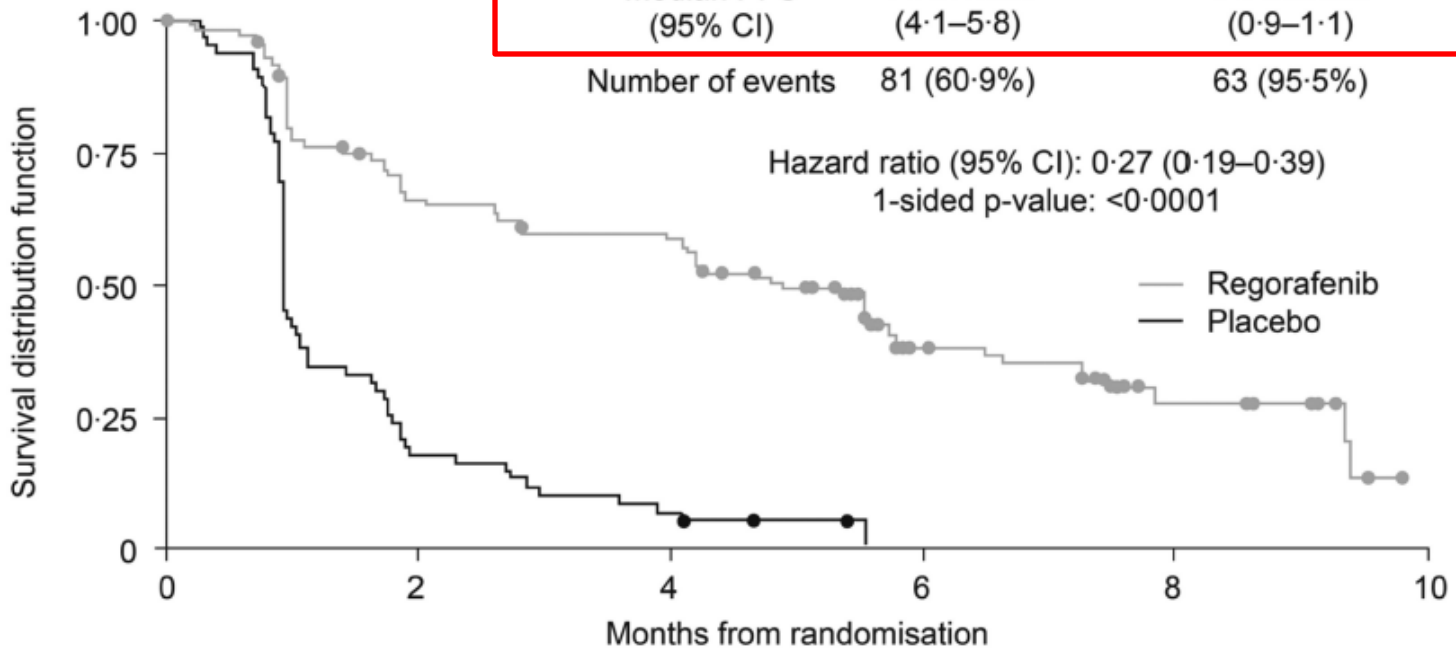
Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicentre, prospective, randomised, placebo-controlled phase 3 trial (GRID)

Response to Regorafenib=Stivarga



Patients at risk				
Regorafenib	82	72	27	9
Placebo	12	5	0	0

	Regorafenib, N=133	Placebo, N=66
Median PFS (95% CI)	4·8 months (4·1–5·8)	0·9 months (0·9–1·1)
Number of events	81 (60·9%)	63 (95·5%)



Patients at risk				
Regorafenib	82	72	27	9
Placebo	12	5	0	0

What about patients who started on placebo and switched to regorafenib ?

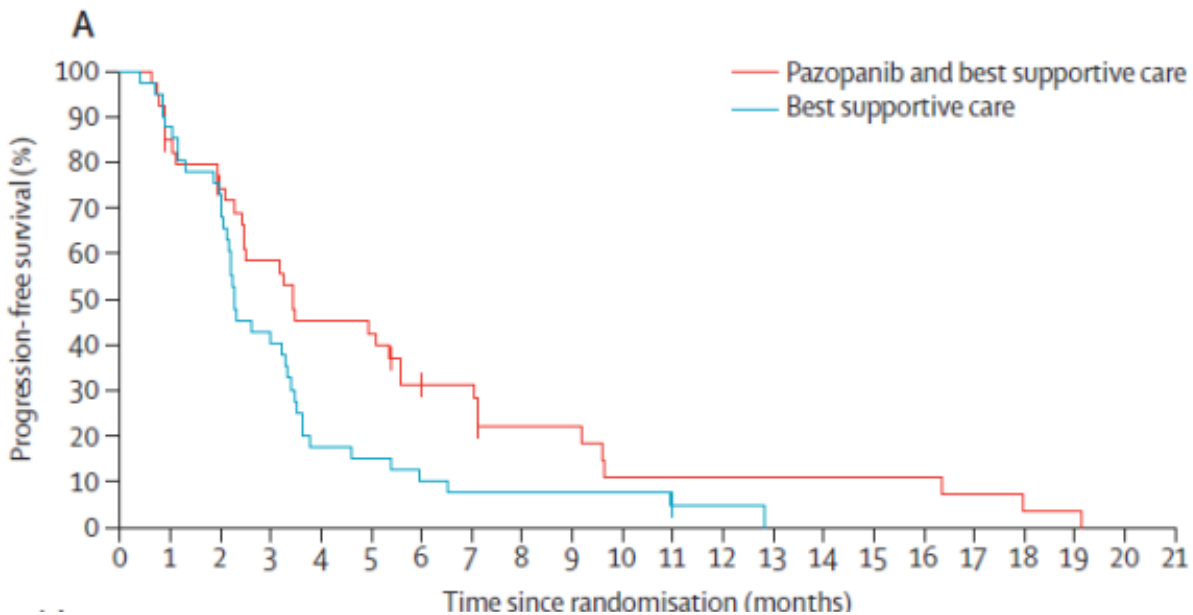
- Median PFS: 5.0 months

NCCN Guidelines Version 2.2016 Soft Tissue Sarcoma

GIST[h]
• Imatinib[25,26] • Sunitinib[27] • Regorafenib[28] Disease progression after imatinib, sunitinib, and regorafenib • Sorafenib[29-31] • Nilotinib[32,33] • Dasatinib[34] (for patients with D842V mutation) • Pazopanib[35]

Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial

Olivier Mir, Claire Cropet, Maud Toulmonde, Axel Le Cesne, Mathieu Molimard, Emmanuelle Bompas, Philippe Cassier, Isabelle Ray-Coquard, Maria Rios, Antoine Adenis, Antoine Italiano, Olivier Bouché, Emmanuelle Chauzit, Florence Duffaud, François Bertucci, Nicolas Isambert, Julien Gautier, Jean-Yves Blay, David Pérol, on behalf of the PAZOGIST study group of the French Sarcoma Groupe-Groupe d'Etude des Tumeurs Osseuses (GSF-GETO)



4 month PFS
45% vs. 17%

MEDIAN PFS
3.4 vs. 2.3 mo
(HR: 0.59, p=0.03)

THANK YOU!