I SIMPOSIO NACIONAL de ONCOLOGÍA de PRECISIÓN

Vigo, del **28** de **febrero** al **1** de **marzo** de **2019**

GIST: Paradigma de medicina de precision.

Dr. Javier Martin-Broto

Disclosure

- **Consulting or Advisory Role**
  - ✓PharmaMar, GSK, Novartis, Amgen, Bayer, Lilly
- **Speakers' Bureau**
  - ✓PharmaMar
- **Research Funding**
  - ✓ Novartis, Eisai, PharmaMar

Gastrointestinal stromal tumor (GIST)

Some figures

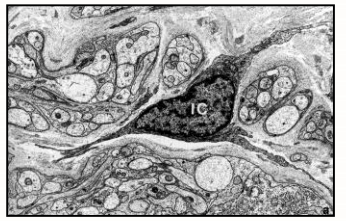
- Most common mesenchymal tumor of the GI-tract
  - Incidence ~10 cases/million/year
- GIST presents localized in 80% of cases (gastric 60%, intestinal 30%)
- GIST is a model of targeted therapies in solid tumors
- High-risk GIST (45%)
  - Consist of large tumors with a high mitotic activity
  - Associated with ≥50% 5-year risk of recurrence after surgery[1-4]

[1]Nilsson B et al. Cancer 2005; 103:821-9; [2]Hassan I et al. Ann Surg Oncol 2008; 15:52-9; [3]Rutkowski P et al. Ann Surg Oncol 2007; 14:2018-27. Martin-Broto Clin Transl Oncol 2017 May;19(5):536-545

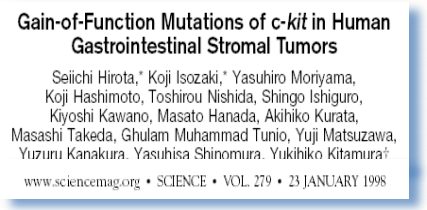
Relevant milestones in GIST (over time)

✓1930-1950: classified as leimyomas, leiomyosarcomas o leiomyoblastomas.
✓1960-1980: Ultraestructural and IHC showed absence of smooth muscle differentiation.
✓1983: Mazur and Clark introduced new term GIST.
✓1994-95: Mesenchymal origen with positivity for CD34.

1998: Kindblom y cols. Precusor Intersticial Cajal Cells cKIT +



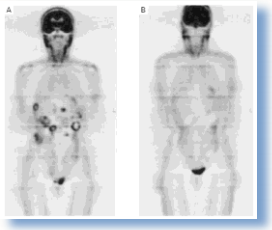
1998: Hirota y cols. Gain-of-function in *KIT* mutations


Gain-of-Function Mutations of c-*kit* in Human Gastrointestinal Stromal Tumors

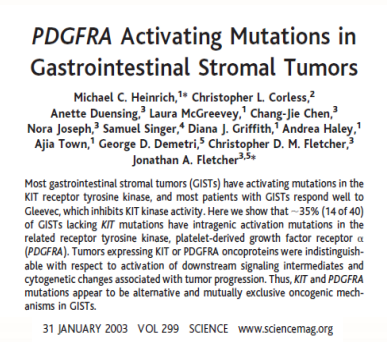
Seiichi Hirota,* Koji Isozaki,* Yasuhiro Moriyama, Koji Hashimoto, Toshirou Nishida, Shingo Ishiguro, Kiyoshi Kawano, Masato Hanada, Akihiko Kurata, Masashi Takeda, Ghulam Muhammad Tunio, Yuji Matsuzawa, Yuzuru Kanakura, Yasuhisa Shinomura, Yukihiko Kitamura†

www.sciencemag.org • SCIENCE • VOL. 279 • 23 JANUARY 1998

2001: Joensuu y cols. Described 1st GIST case treated with IMATINIB



2003: Heinrich y cols. described another driver in GIST: PDGFRα.


PDGFRA Activating Mutations in Gastrointestinal Stromal Tumors

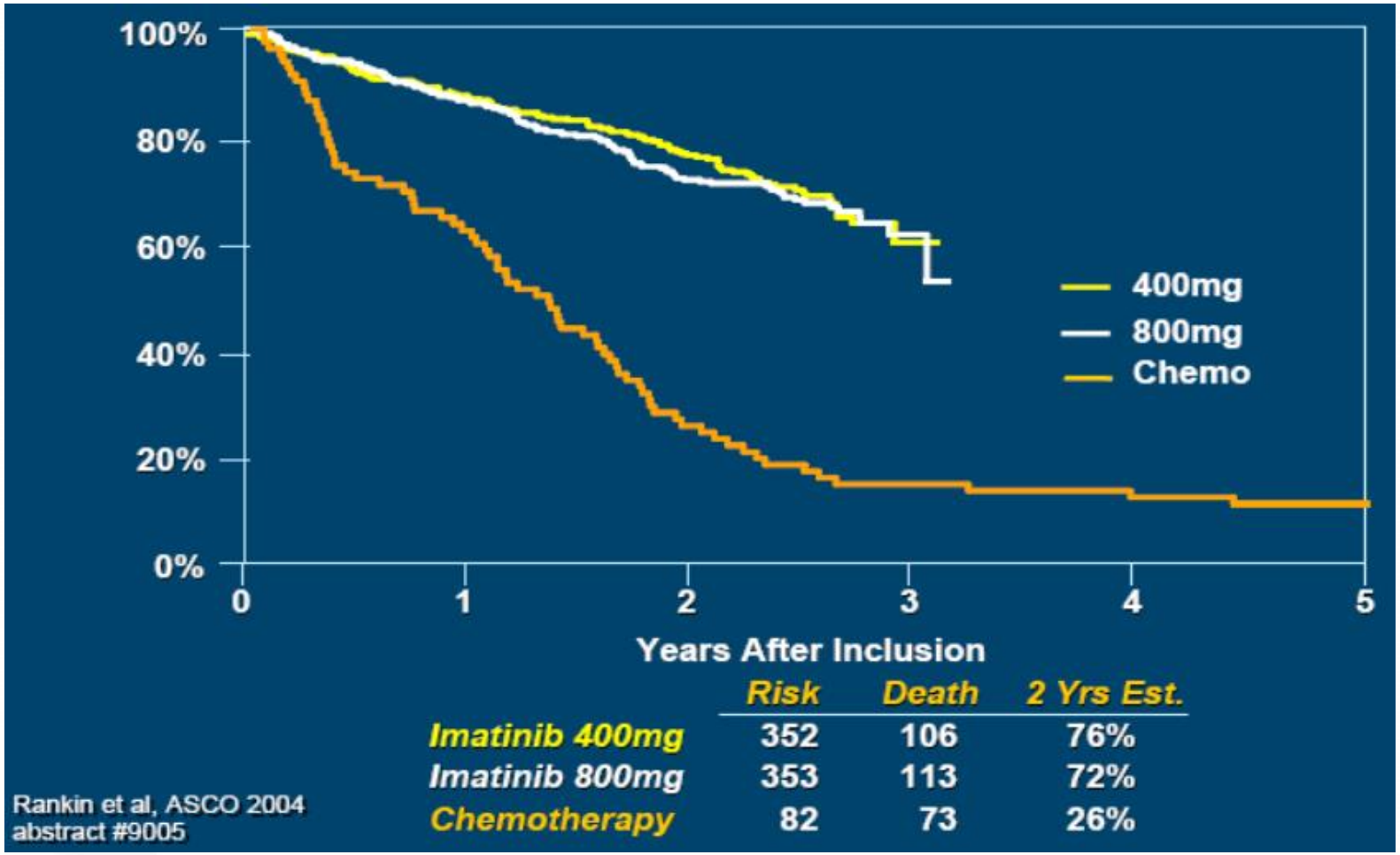
Michael C. Heinrich,[1*] Christopher L. Corless,[2] Anette Duensing,[3] Laura McGreevey,[1] Chang-Jie Chen,[3] Nora Joseph,[3] Samuel Singer,[4] Diana J. Griffith,[1] Andrea Haley,[1] Ajia Town,[1] George D. Demetri,[5] Christopher D. M. Fletcher,[3] Jonathan A. Fletcher[3,5*]

Most gastrointestinal stromal tumors (GISTs) have activating mutations in the KIT receptor tyrosine kinase, and most patients with GISTs respond well to Gleevec, which inhibits KIT kinase activity. Here we show that ~35% (14 of 40) of GISTs lacking *KIT* mutations have intragenic activation mutations in the related receptor tyrosine kinase, platelet-derived growth factor receptor α (*PDGFRA*). Tumors expressing KIT or PDGFRA oncoproteins were indistinguishable with respect to activation of downstream signaling intermediates and cytogenetic changes associated with tumor progression. Thus, *KIT* and *PDGFRA* mutations appear to be alternative and mutually exclusive oncogenic mechanisms in GISTs.

31 JANUARY 2003 VOL 299 SCIENCE www.sciencemag.org

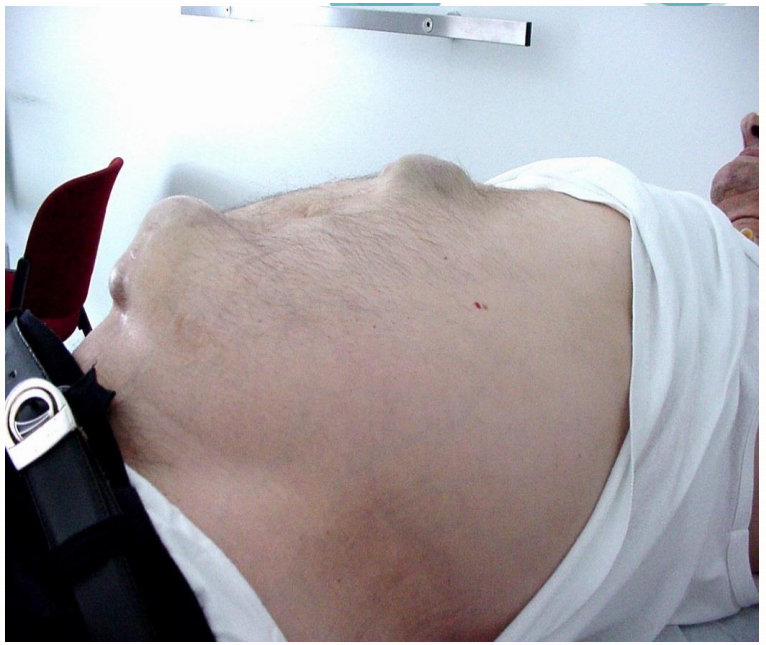
Change of Expectations

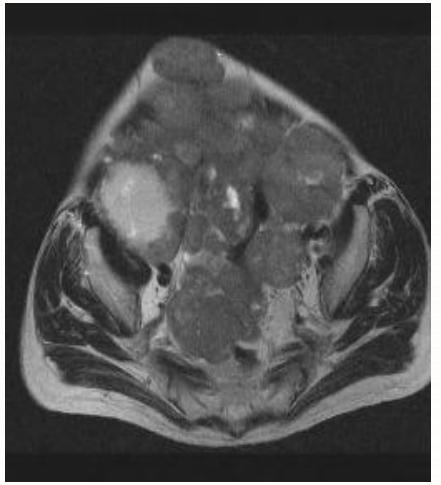
Life expectancy < 1 year to > 5 years



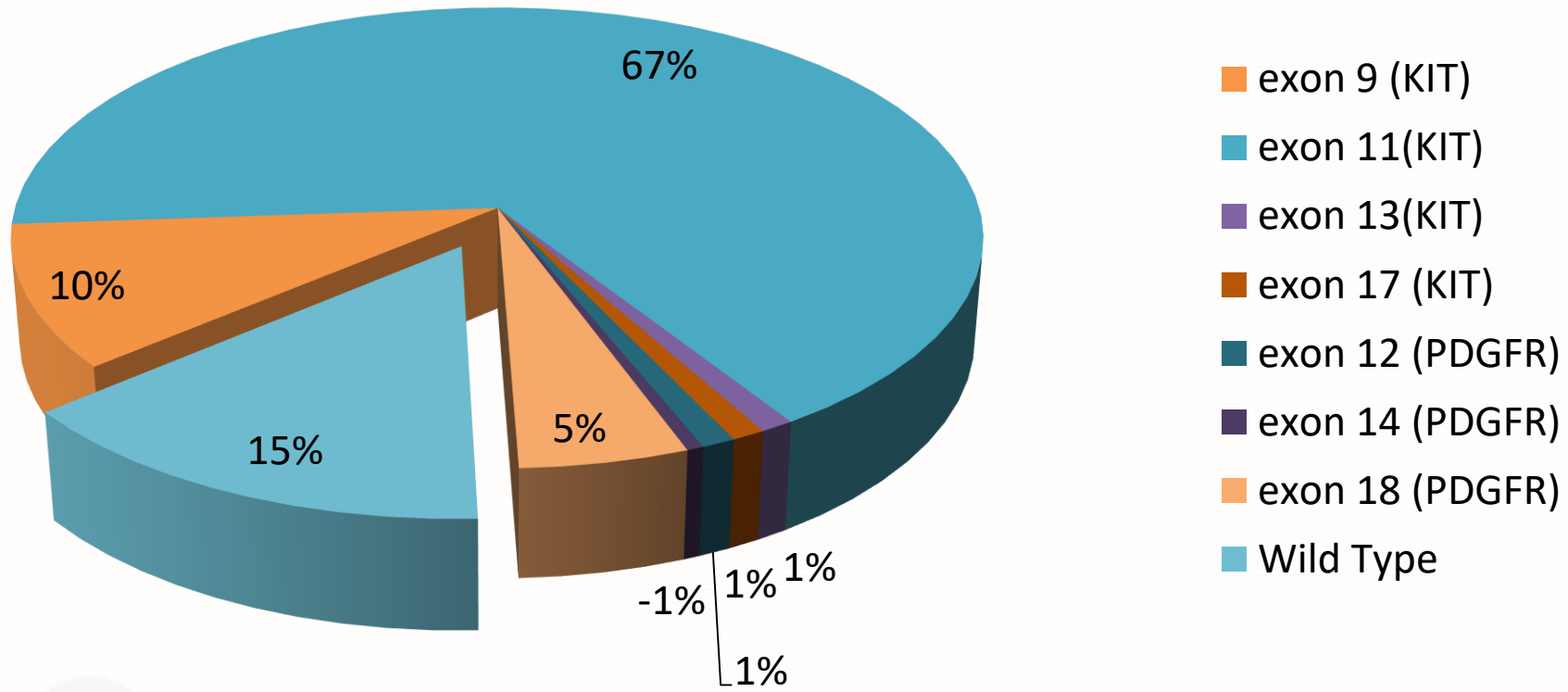
	Risk	Death	2 Yrs Est.
Imatinib 400mg	352	106	76%
Imatinib 800mg	353	113	72%
Chemotherapy	82	73	26%

Rankin et al, ASCO 2004 abstract #9005

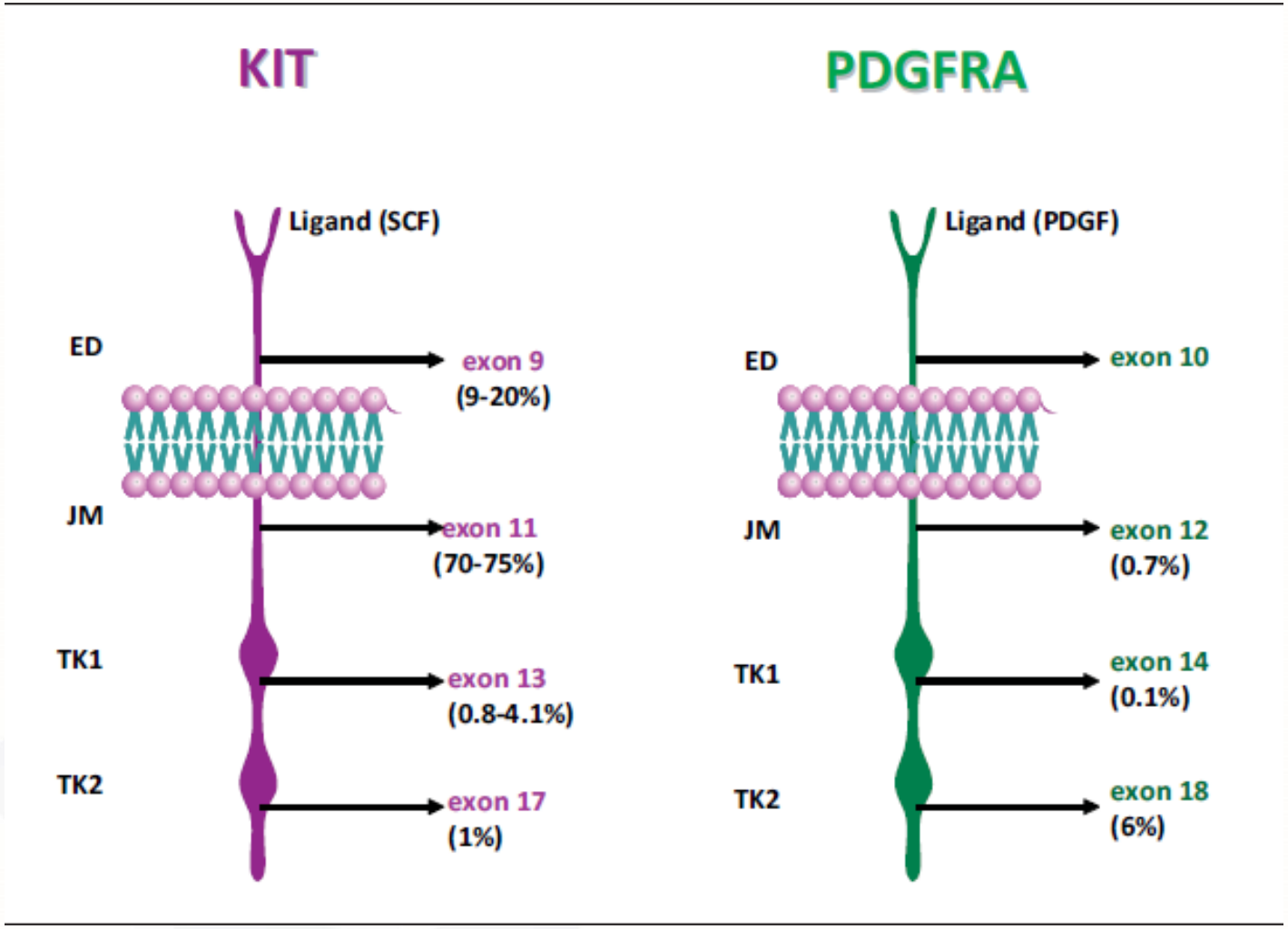




Molecular Classification of GIST
Genotype



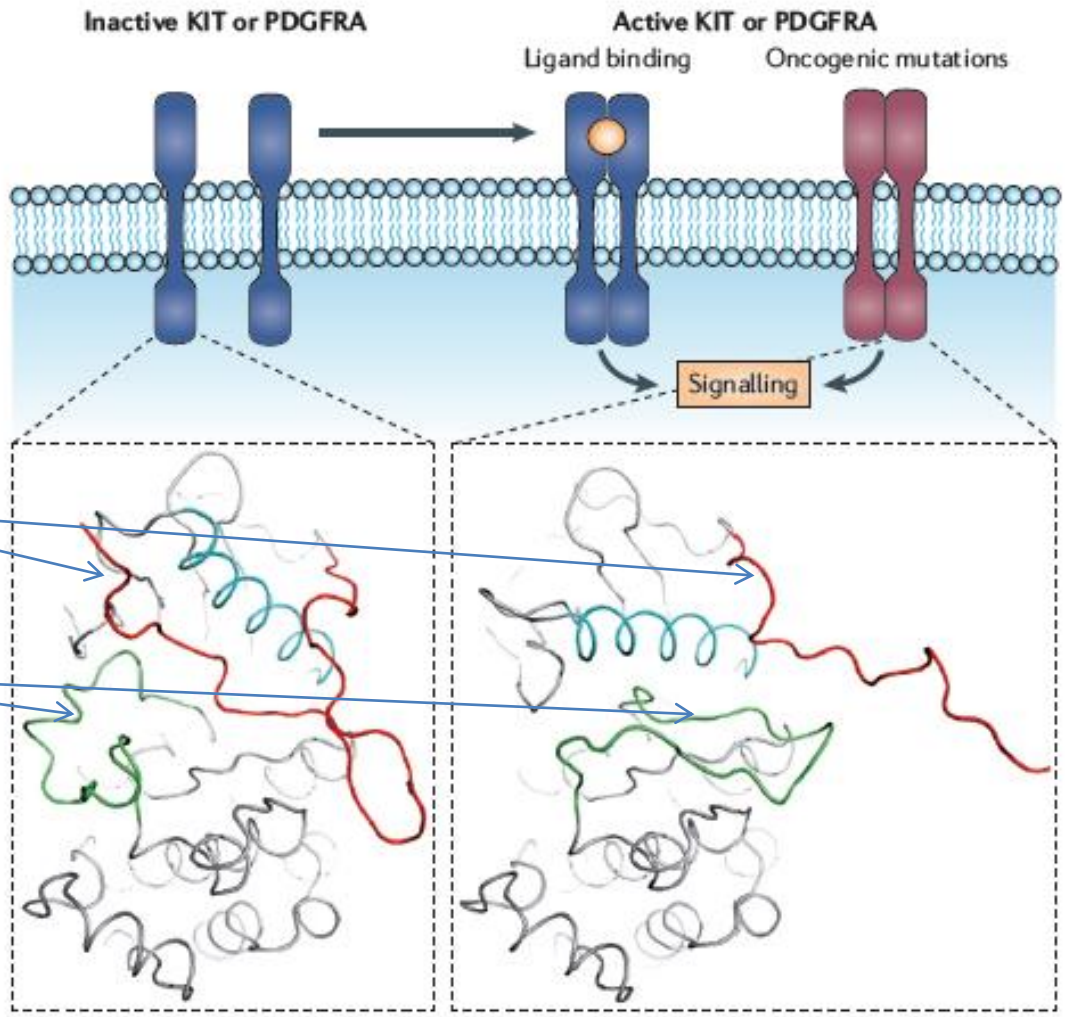
GENOTYPE IN GIST



- Genes codifying KIT & PDGFRa map to chromosome 4q12
- Type III TKR (highly homologous)
- Extracellular domain: binding ligand and dimerization
- Cytoplasmic domain
  - Juxtamembrane
  - TK domains

Histopathology 2008, 53:255

KIT & PDGFRA DRIVERS

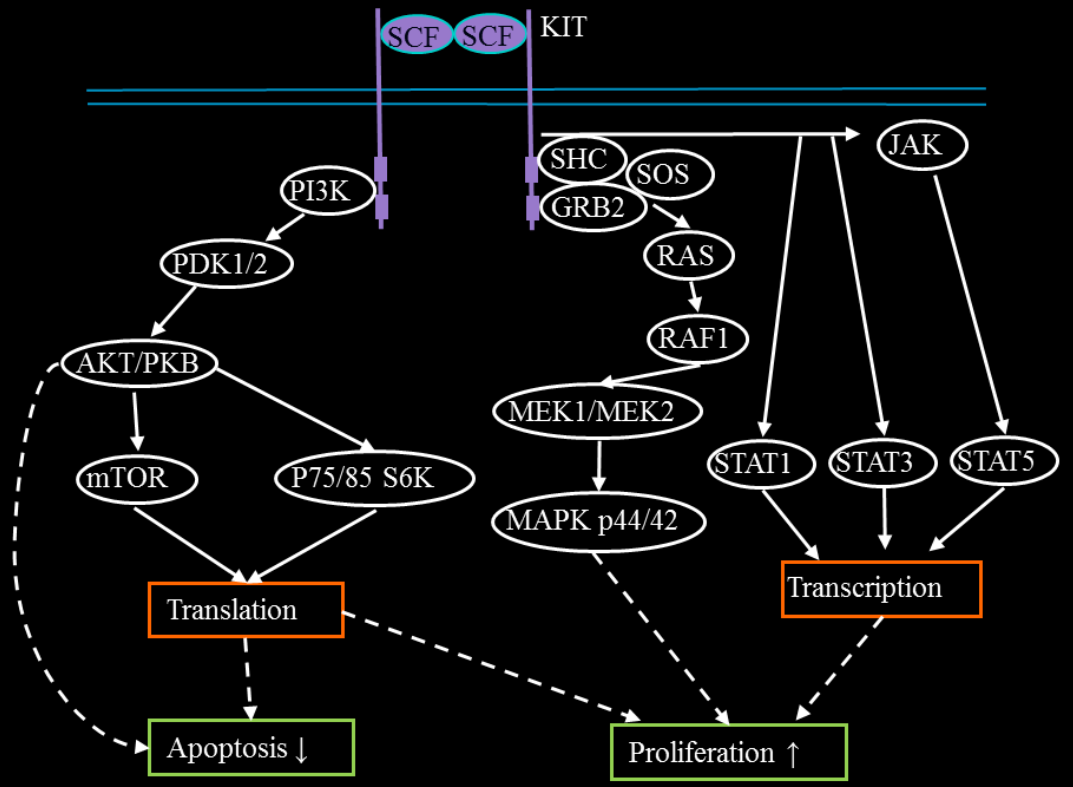


Juxtamembrane domain

Activation loop

Proc. Natl Acad. Sci. USA **106**, 1542–1547 (2009).

KIT downstream signalling



- Mutations of KIT and PDGFRA RTKs increase cell proliferation while decreasing apoptosis
- Downstream signaling pathways of mutant KIT or PDGFRA are thought to be similar, although specific gene expression differs

PDGFRA=platelet-derived growth factor receptor-alpha; PI3K=phosphoinositide 3-kinase; RTK=receptor tyrosine kinase; SCF=stem cell factor.

Mutation analysis: KIT and PDGFRA page. GIST Support International Website. http://www.gistsupport.org/about-gist/mutation-analysis-kit-and-pdgfra.php. Accessed 08/23/2010.

MUTATIONS AS PROGNOSTIC FACTORS

Risk Assessment in Localized GIST

FLETCHER

50 HPF=
10-12 mm^2

	Size	Mitotic Count (50 hpf)
Very Low Risk	< 2 cm	≤ 5 mitoses
Low Risk	2-5 cm	≤ 5 mitoses
Intermediate Risk	≤ 5 cm 5-10 cm	6-10 mitoses ≤ 5 mitoses
High Risk	> 5 cm > 10 cm Any size	> 5 mitoses Any mitotic count > 10 mitosis

Fletcher CD et al. Hum Pathol. 2002; 33:459-65

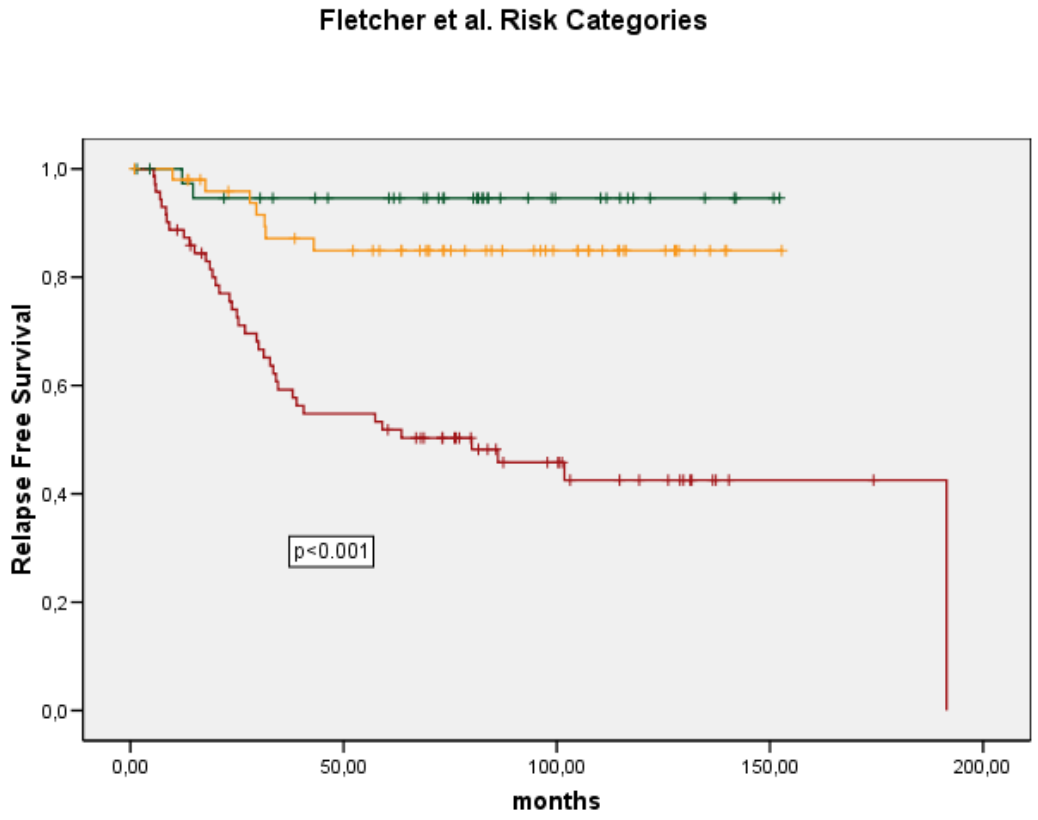
MIETTINEN-LASOTA

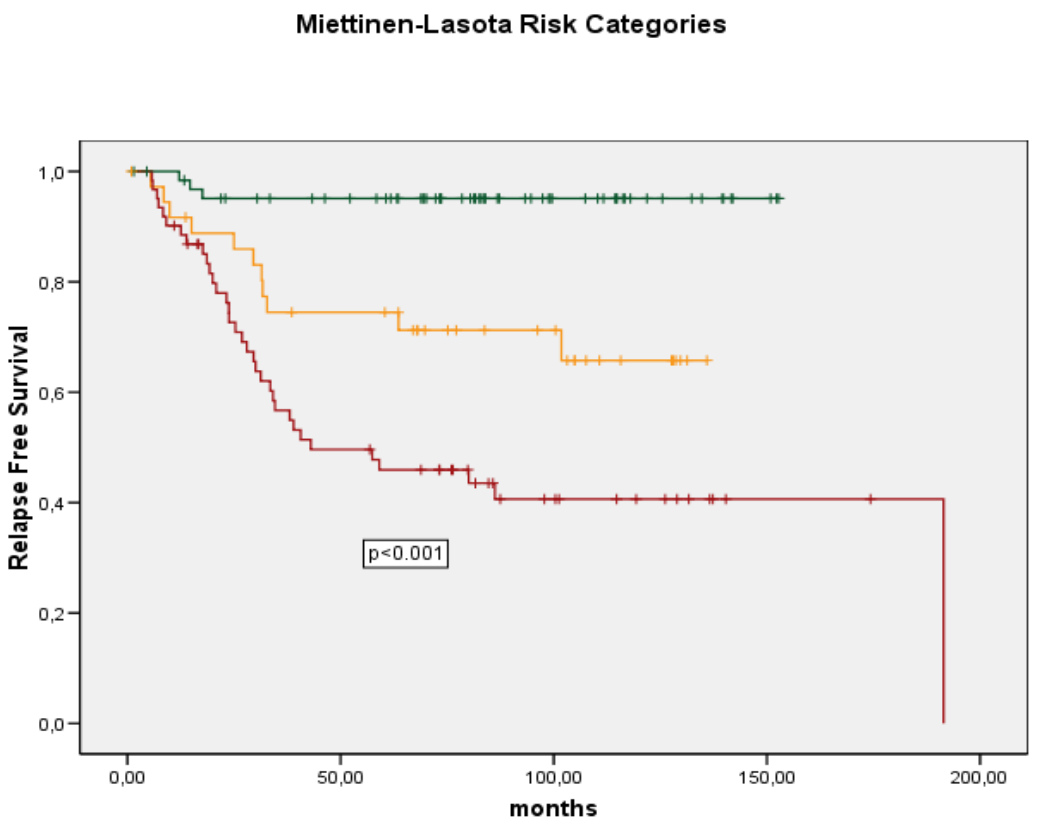
50 HPF=
5 mm^2

	Size	Mitotic count (50 hpf)	Location
Very Low Risk	2- 5 cm	≤ 5 mitoses	gastric
Low Risk	>5 ≤ 10 cm 2- 5 cm	≤ 5 mitoses ≤ 5 mitoses	gastric intestinal
Intermediate Risk	>10 cm >5 y ≤ 10 cm 2- 5 cm	≤ 5 mitoses ≤ 5 mitoses > 5 mitoses	gastric intestinal gastric
High Risk	2- 5 cm > 10 cm	> 5 mitoses ≤ 5 mitoses	intestinal intestinal
	>5 y ≤ 10 cm > 10 cm	> 5 mitoses > 5 mitoses	gastric gastric
	>5 y ≤ 10 cm > 10 cm	> 5 mitoses > 5 mitoses	intestinal intestinal

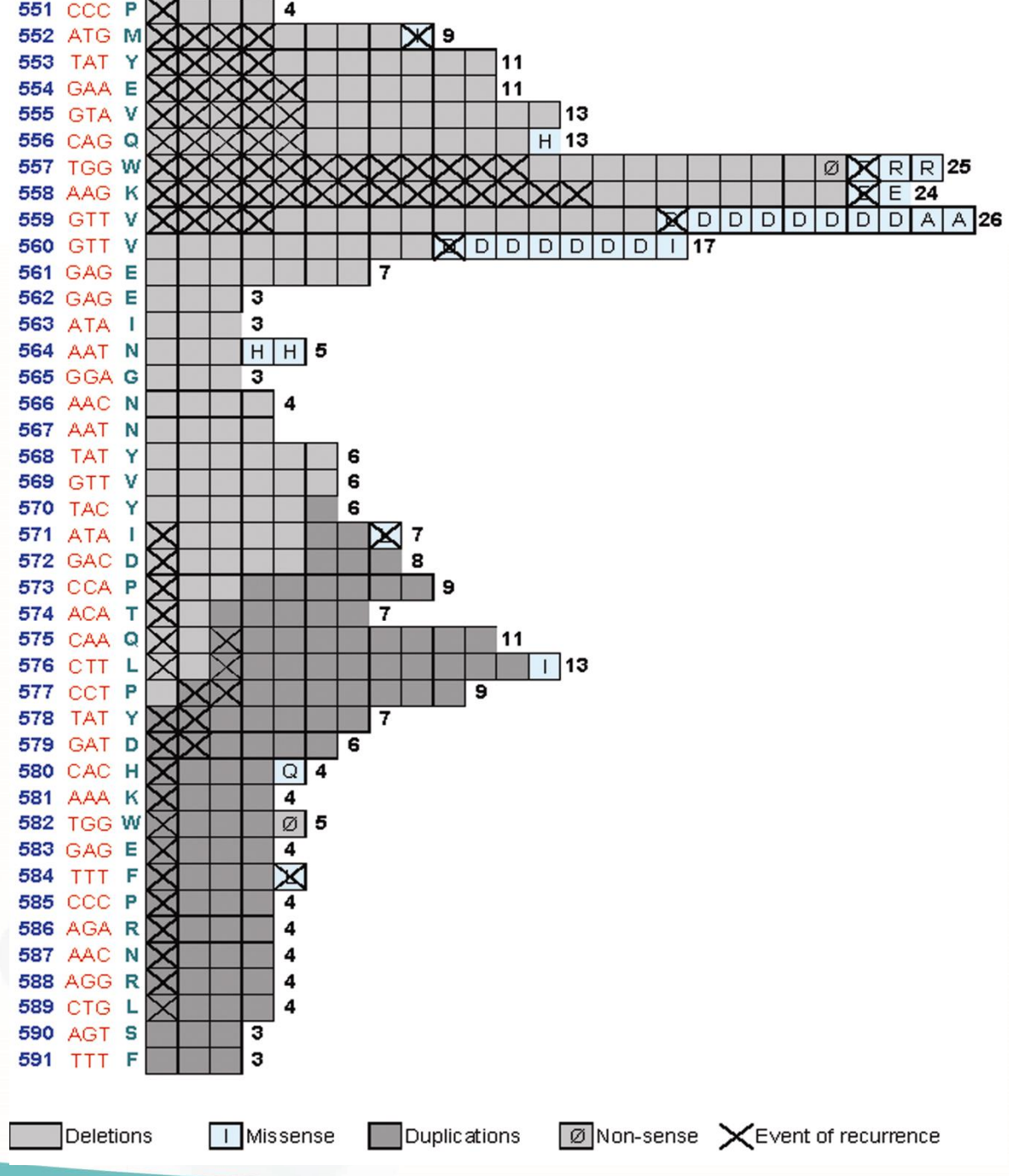
Miettinen M, Lasota J. Semin Diagn Pathol. 2006 May;23(2):70-83

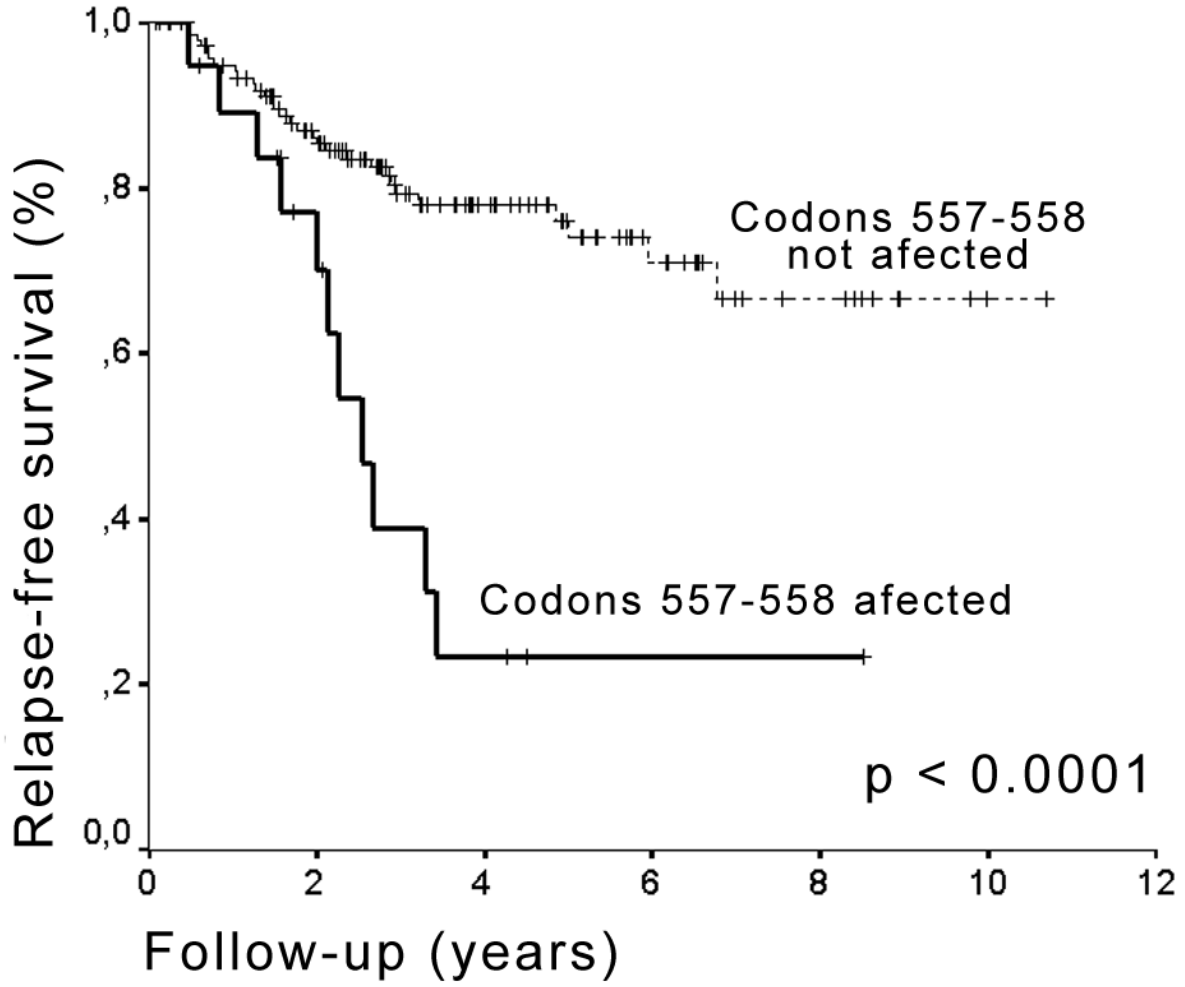
Risk Stratification





J Martin-Broto et al. Ann Oncol 21: 2010; 1552-1557





J Martin et al. J Clin Oncol 2005 Sep 1;23(25):6190-8.

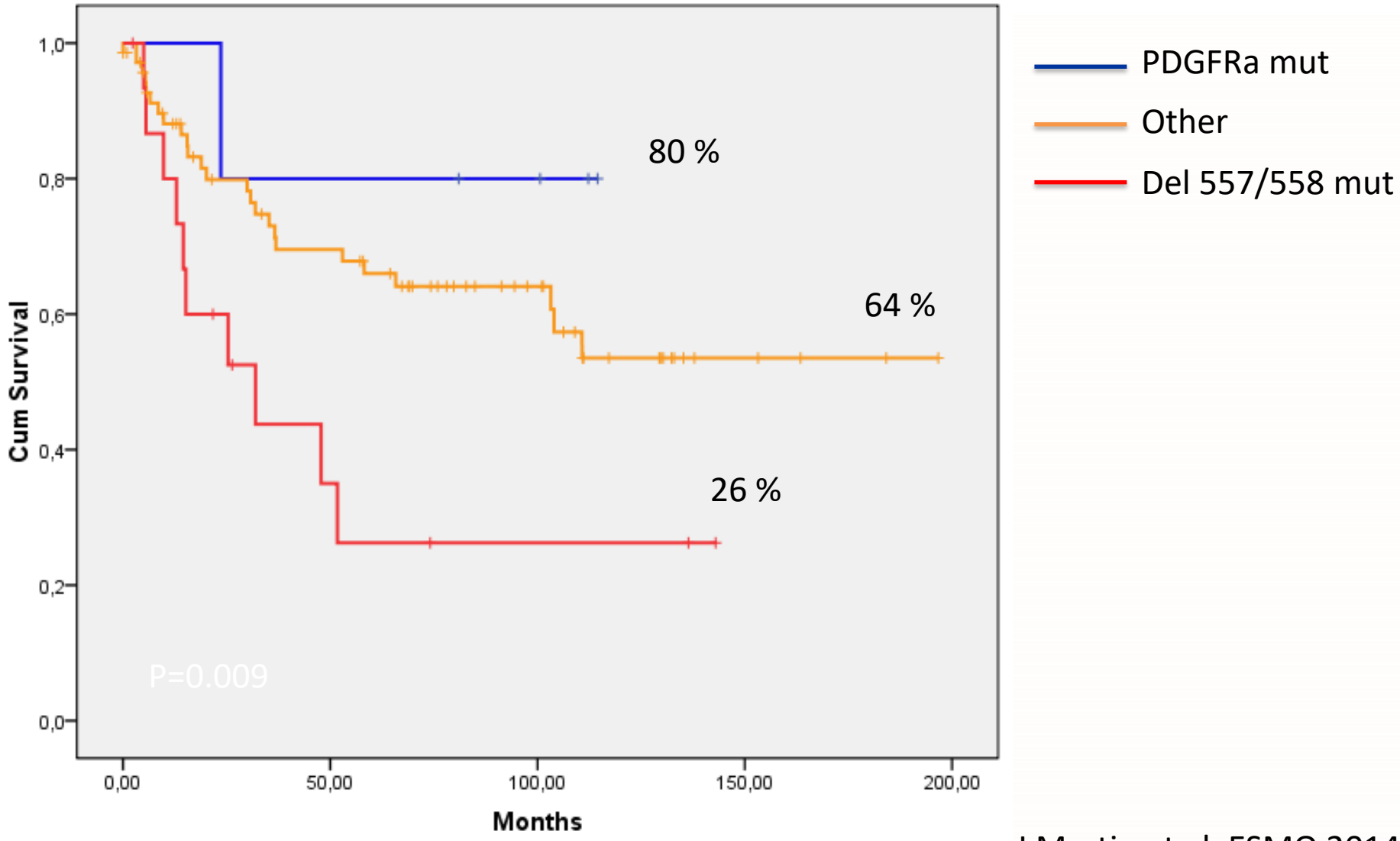
Independent prognostic factors for RFS in GIST patients
Multivariate analysis

Factors	RR	95%CI	p
Miettinen-Lasota Risk Categories:			
Intermediate	5.97	2.09-17.06	0.001
High	11.45	4.40-29.76	<0.001
Critical Mutations 557 or 558	3.05	1.59-5.85	0.001

J Martin et al, ASCO 2008, oral presentation

J Martin et al, Ann Oncol. 2010 Jul; 21(7):1552-7

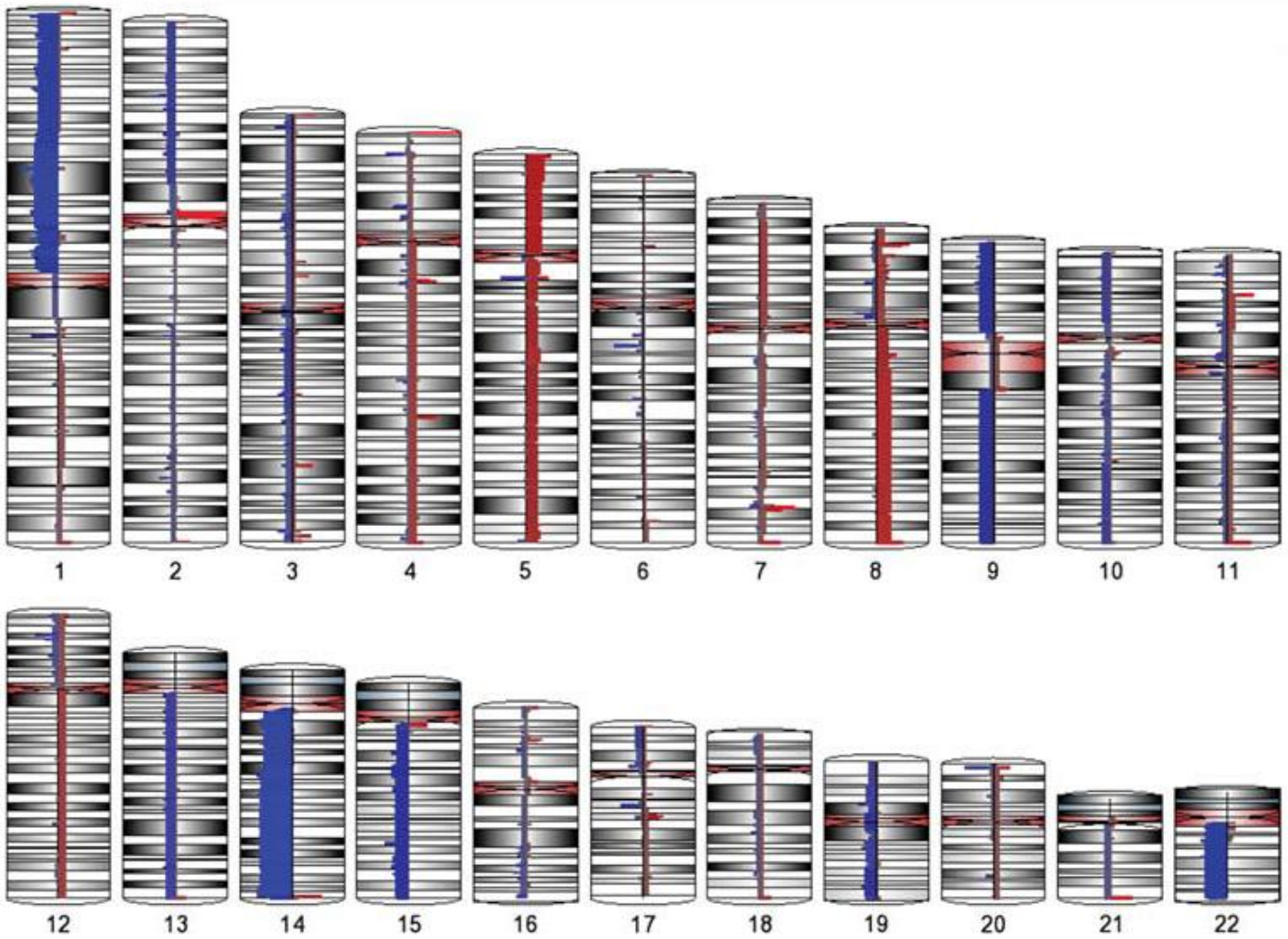
7-year ACTUARIAL RFS IN INTERMEDIATE RISK MIETTINEN CLASSIFICATION
According to prognostic genotype



J Martin et al, ESMO 2014

GIST GENETIC PROGRESSION

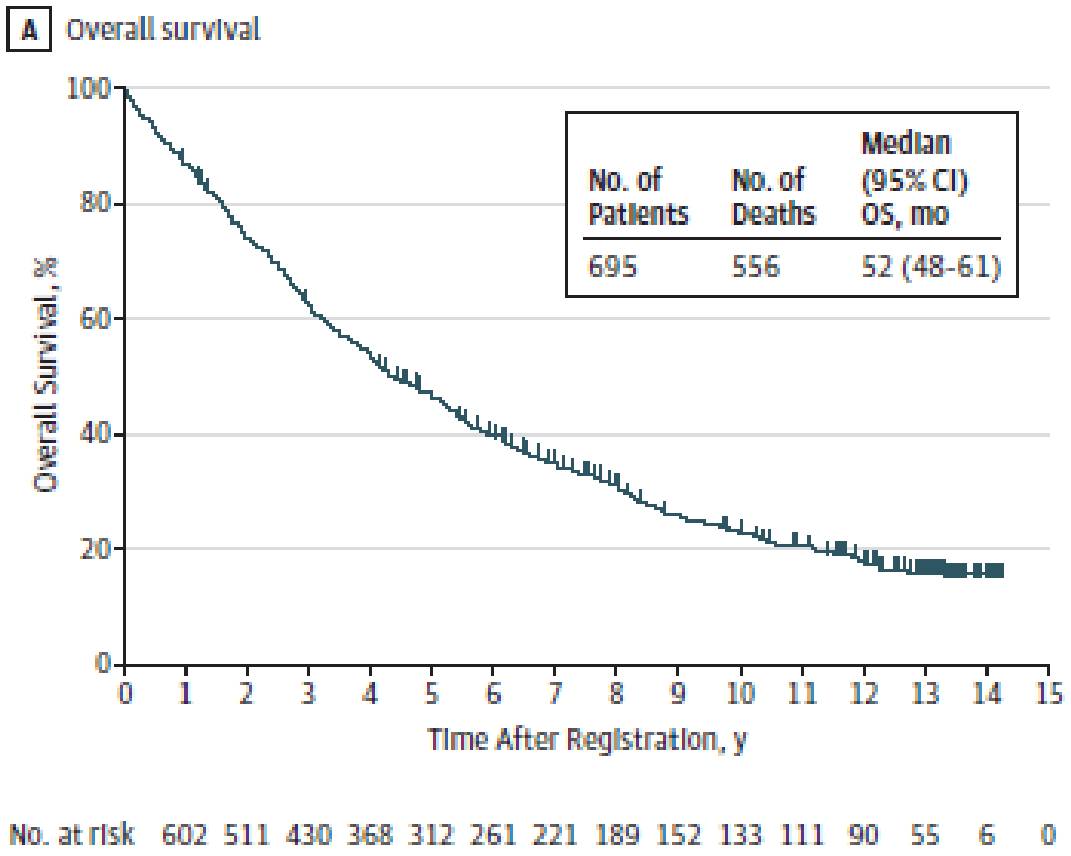
KIT or *PDGFRa* mutations 14q→ 22q→1p

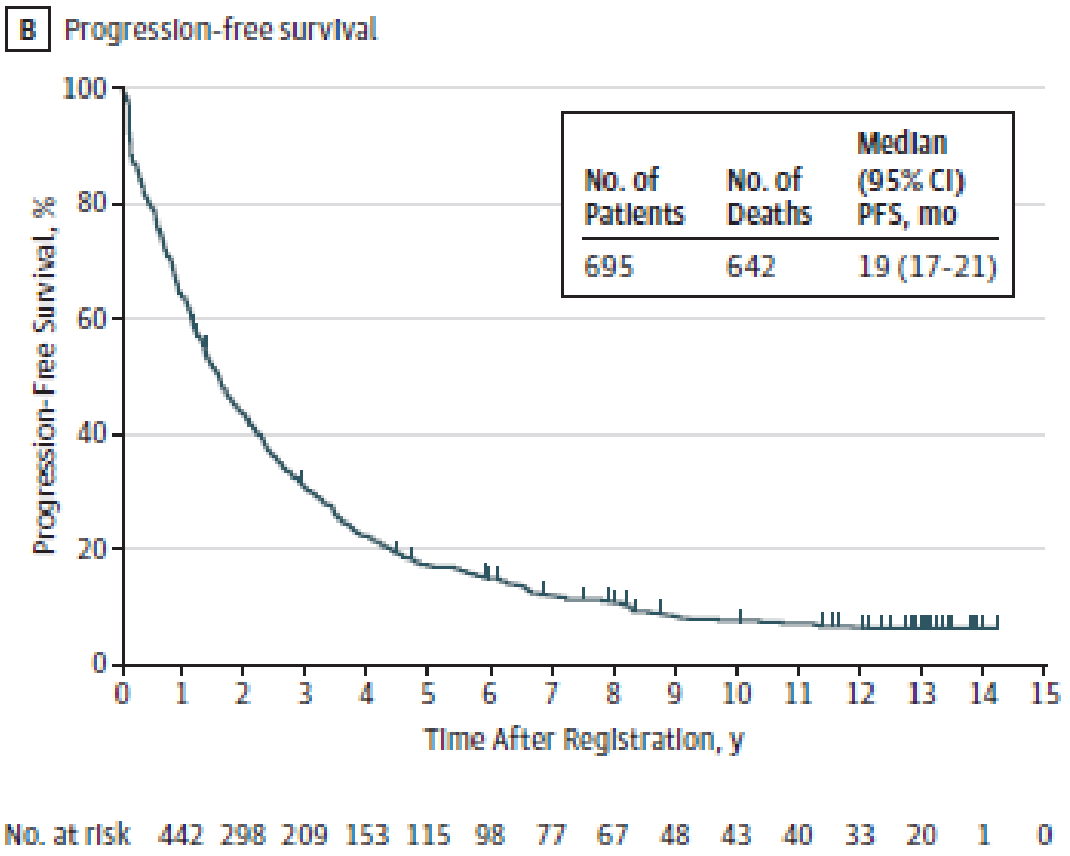


A Astolfi, Lab Invest 90, 2010

MUTATIONS AS PREDICTIVE FACTORS

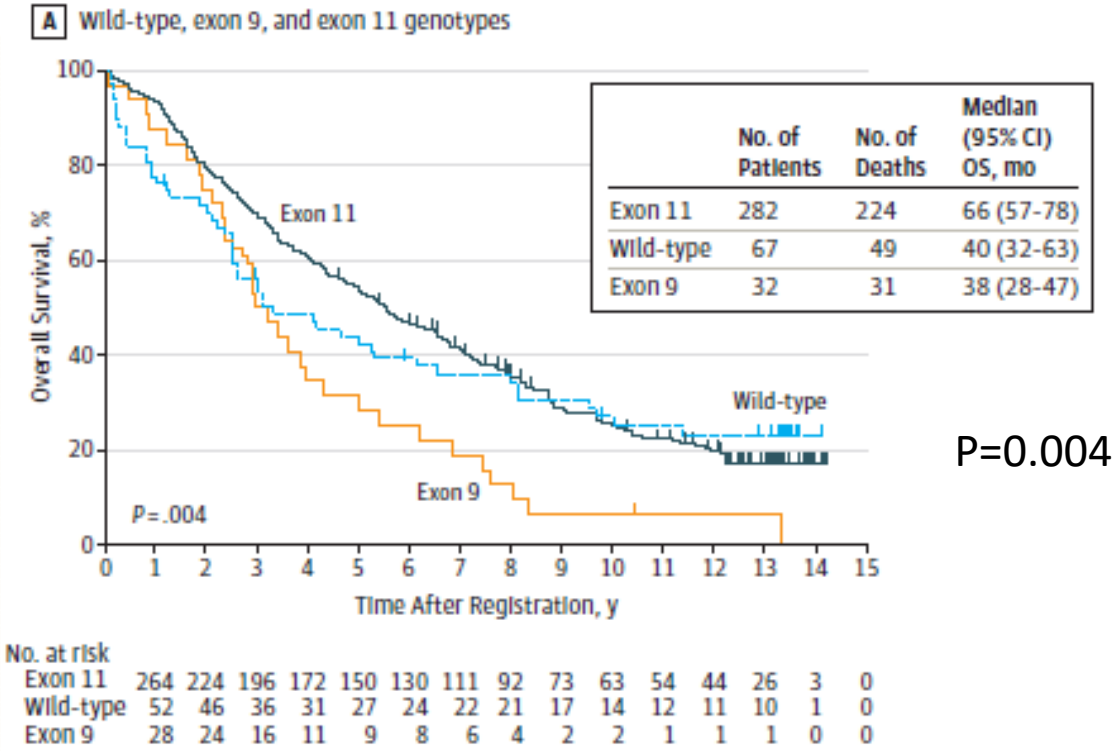
Long-term KM curves first line





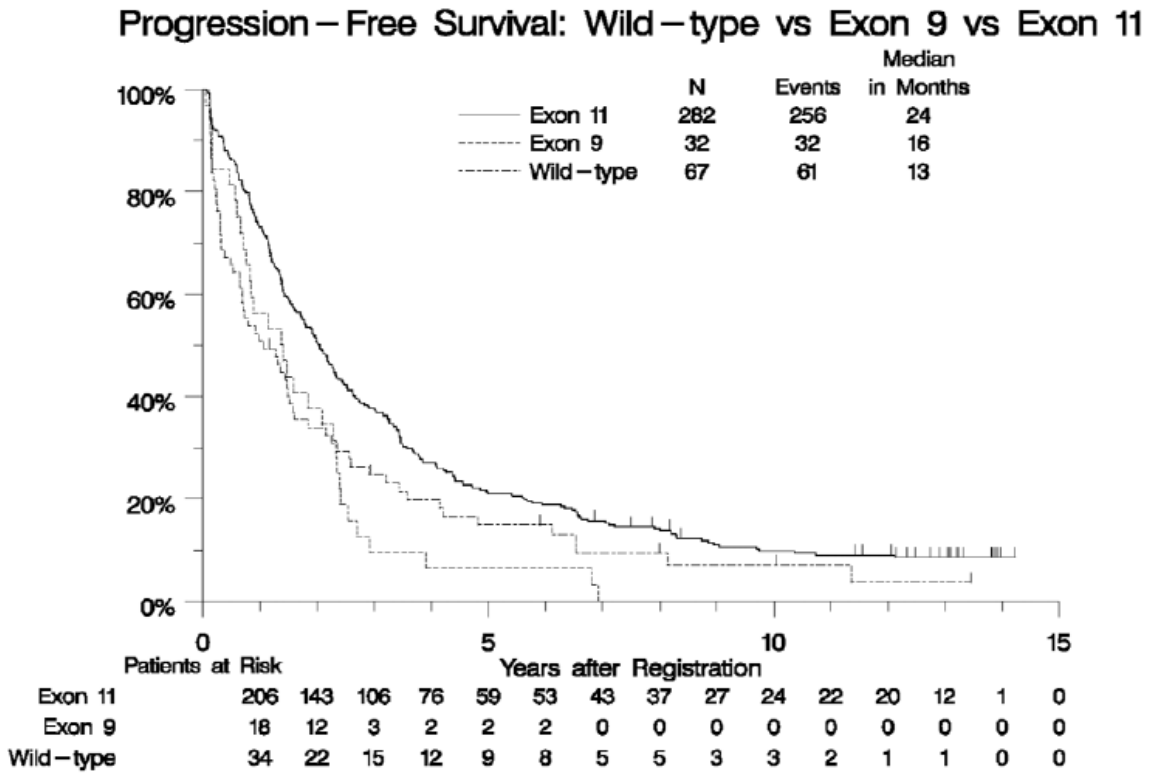
M Heinrich, *JAMA Oncol*. 2017;3(7):944-952.

GENOTYPE & OUTCOME IN FIRST LINE



	No. of Patients	No. of Deaths	Median (95% CI) OS, mo
Exon 11	282	224	66 (57-78)
Wild-type	67	49	40 (32-63)
Exon 9	32	31	38 (28-47)

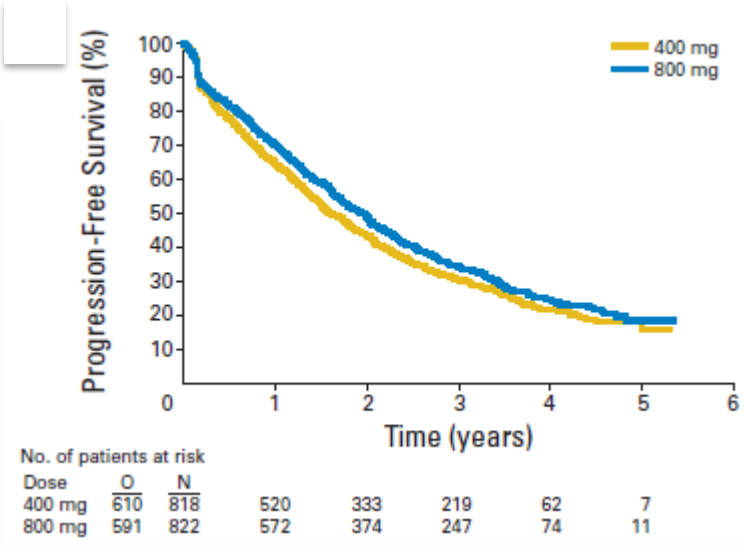
P=0.004



M Heinrich, *JAMA Oncol*. 2017;3(7):944-952.

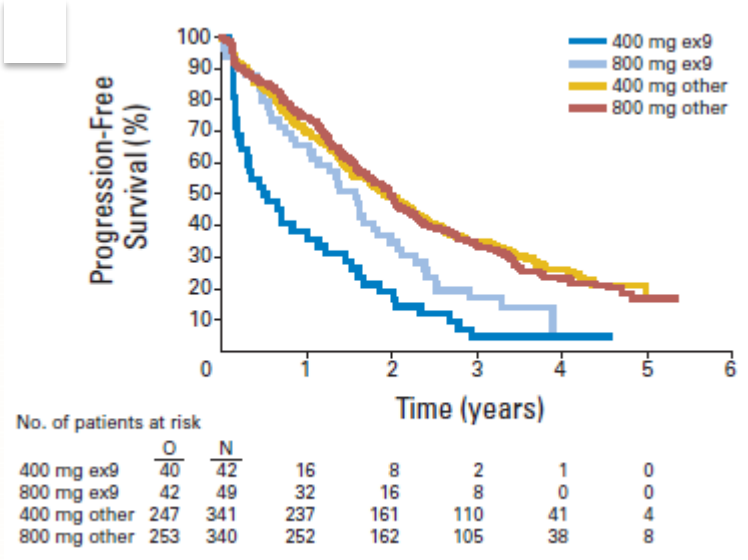
EXON 9 mutants & Imatinib dose

META GIST. N = 1640



No. of patients at risk

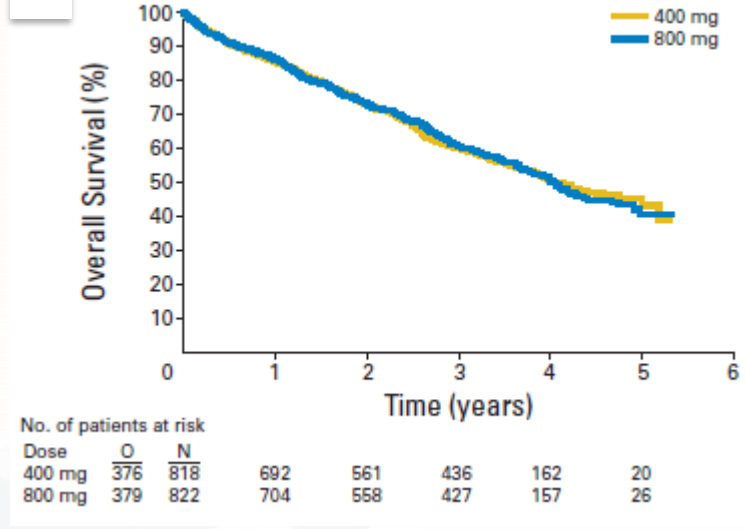
Dose	O	N					
400 mg	610	818	520	333	219	62	7
800 mg	591	822	572	374	247	74	11



No. of patients at risk

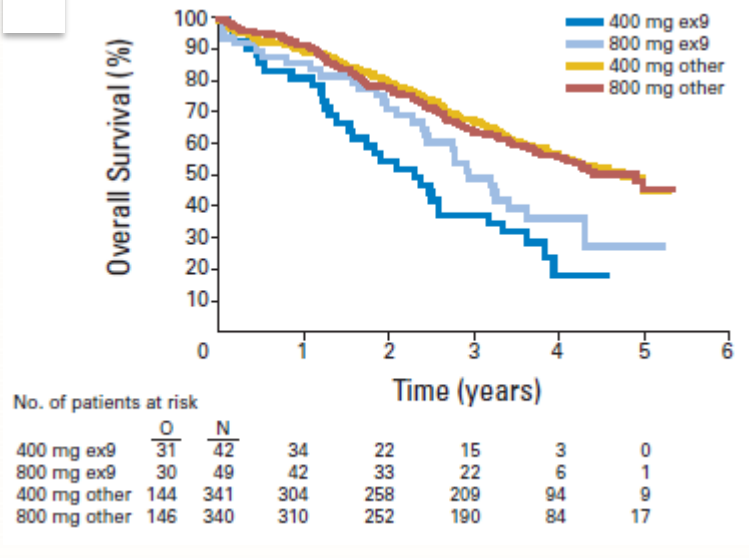
	O	N					
400 mg ex9	40	42	16	8	2	1	0
800 mg ex9	42	49	32	16	8	0	0
400 mg other	247	341	237	161	110	41	4
800 mg other	253	340	252	162	105	38	8

P= 0.012



No. of patients at risk

Dose	O	N					
400 mg	376	818	692	561	436	162	20
800 mg	379	822	704	558	427	157	26



No. of patients at risk

	O	N					
400 mg ex9	31	42	34	22	15	3	0
800 mg ex9	30	49	42	33	22	6	1
400 mg other	144	341	304	258	209	94	9
800 mg other	146	340	310	252	190	84	17

P= 0.15

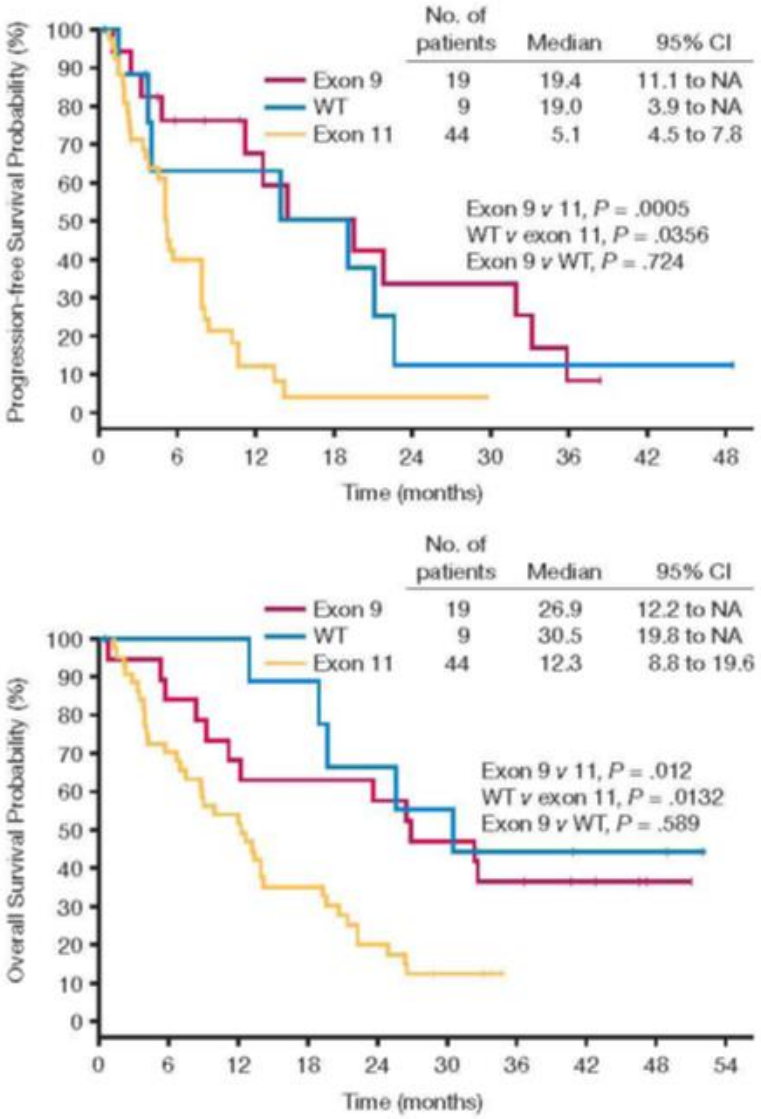
Van Glabbeke et al. *J Clin Oncol 2010, 28:1247-1253.*

Landscape in Imatinib Resistant

Drug	Clinical trial	Setting	ORR (%)	mPFS (mo)	Phase
Sunitinib	Demetri, 2006	2nd line	7	6.1	Approved
Regorafenib	Demetri, 2013	3rd line	4.5	4.8	Approved
Dovitinib	Kang, 2013	≥ 3rd line	3	3.6	II
	Joensuu, 2014	≥ 3rd line	5	4.6	II
Masitinib	Adenis, 2014	2nd line	N.A.	3.7	II
Nilotinib	Montemurro, 2009	≥ 3rd line	10	2.8	II
	Sawaki, 2011	3rd line	3	3.7	II
	Cauchi, 2012	≥ 3rd line	0	2.0	II
	Reichardt, 2012	3rd line	<1	3.6	III
Pazopanib	Ganjoo, 2014	≥ 2nd line	0	1.9	II
	Mir, 2016	≥ 2nd line	0	3.4	II
Ponatinib*	Heinrich, 2015	≥ 2nd line	8	4.3	II
Sorafenib	Kindler, 2011	≥ 2nd line	13	5.2	II
	Park, 2012	≥ 3rd line	13	4.9	II

Serrano et al, *Target Oncol 2017*

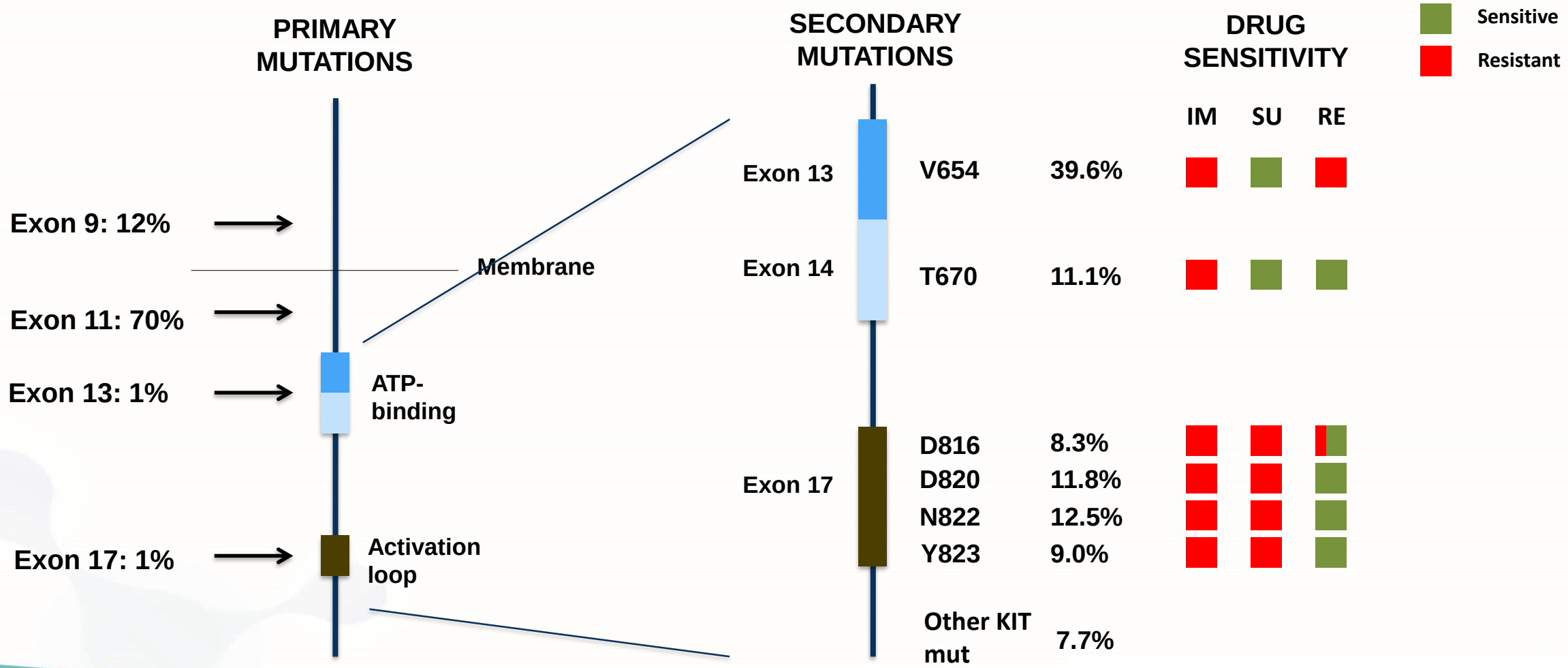
Primary genotype and 2nd line



PRIMARY GENOTYPE (pre-Imatinib) AND SUNITINIB EFFICACY

R Maki et al, Abstract #9011, ASCO 2005
M Heinrich et al J Clin Oncol 2008, 26:5352-5359

KIT/PDGFRA genotype predicts response to TKI



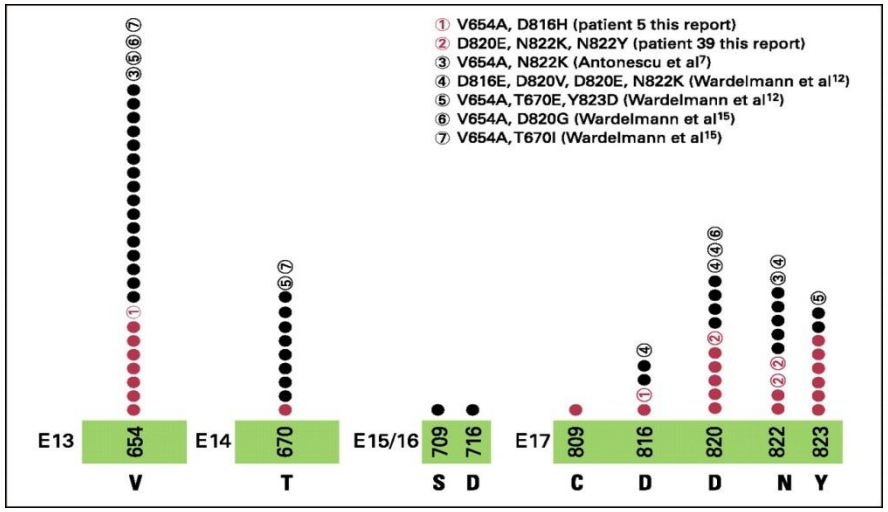
Serrano et al, Br J Cancer 2019 *in press*

Tumor Heterogeneity

→ Molecular heterogeneity at progression

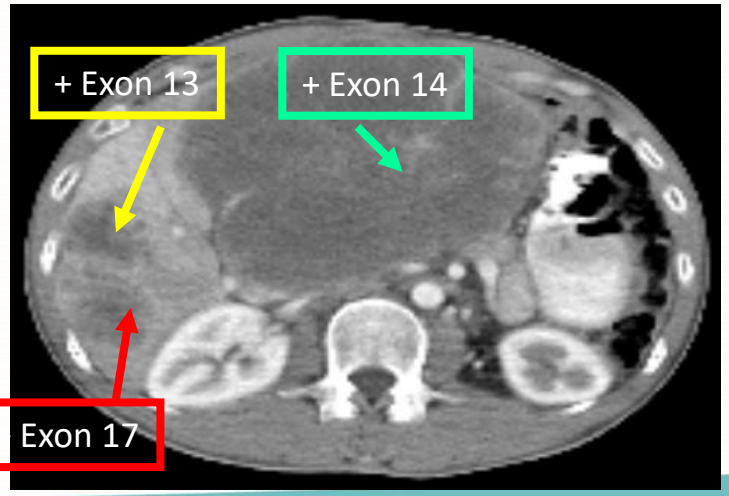
– After imatinib

Debiec Rychter et al, Heinrich et al 2006



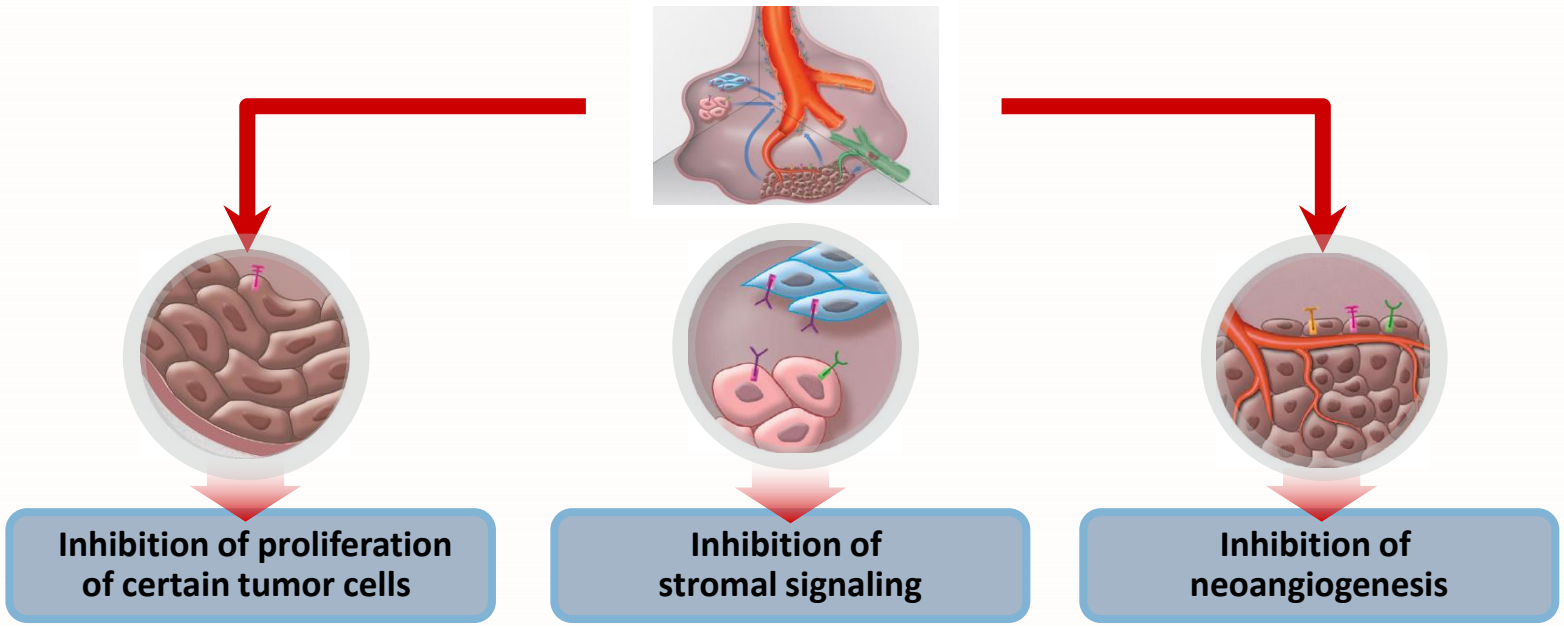
– After sunitinib

Fletcher et al ECCO 2007



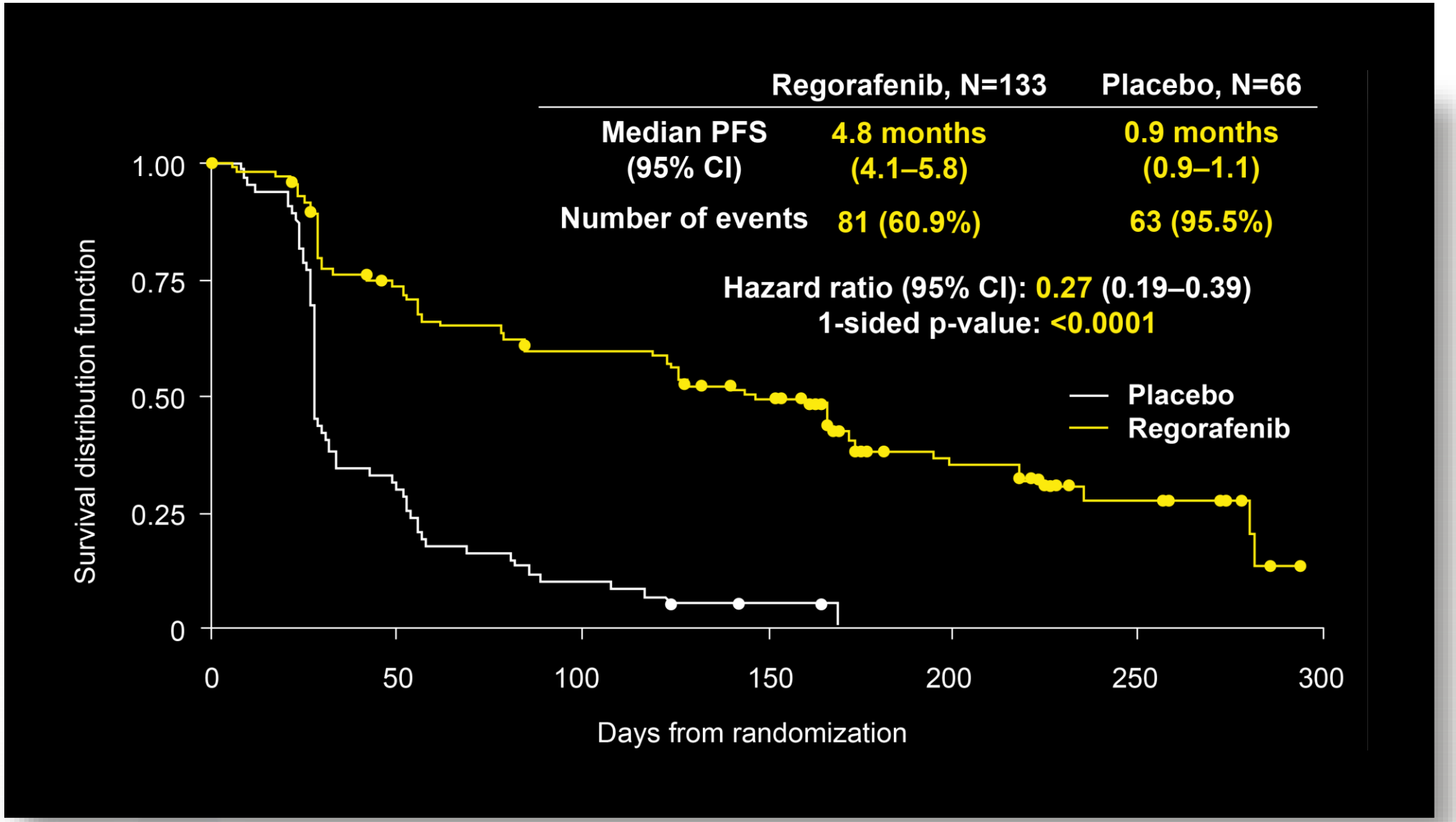
Exon 11 mutation

Mode of action of Regorafenib (BAY 73-4506)



- **Regorafenib is an oral multikinase inhibitor with a distinct profile targeting:**
  - **angiogenic (VEGFR1-3, TIE2)**
  - **stromal (PDGFR-β, FGFR)**
  - **oncogenic (KIT, PDGFR and RET) receptor tyrosine kinases**

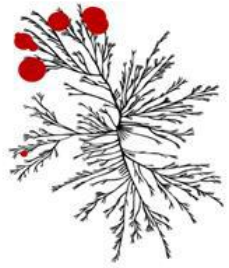
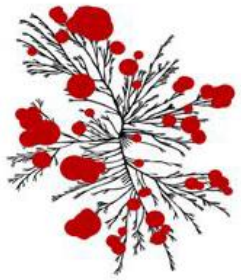
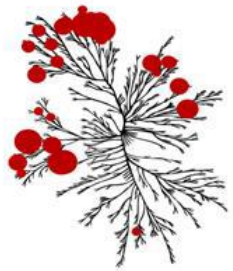
Regorafenib Pivotal Trial



Regorafenib significantly improved PFS *vs* placebo (p<0.0001); primary endpoint met

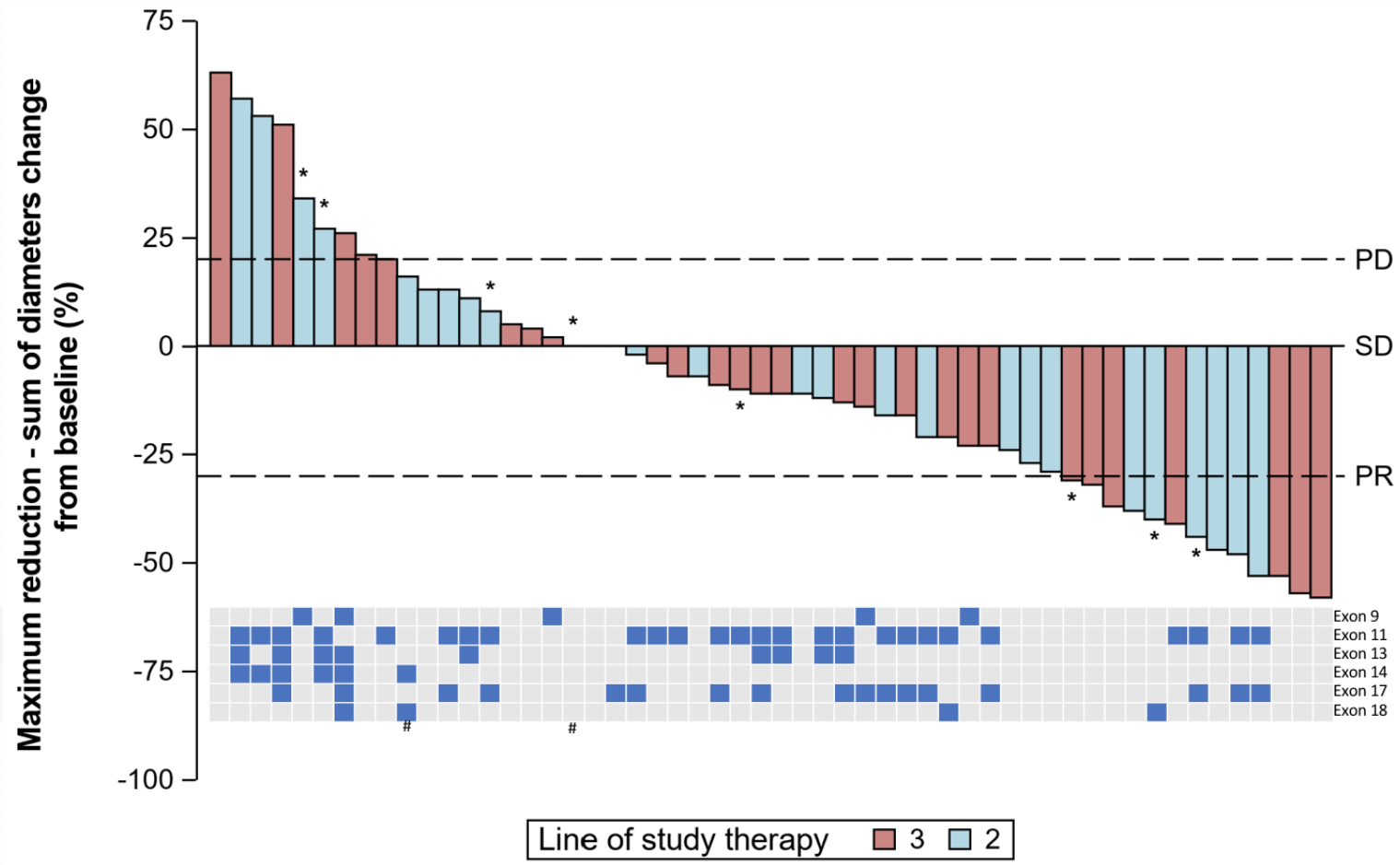
Lancet 2013,381(9863):295-302

HOW TO IMPROVE THE OUTCOME IN GIST

	mPFS	mOS/ 6mOS
imatinib 	20	52 (mOS)
sunitinib 	6.8	79.4% (6mOS)
regorafenib 	4.8	78.0% (6mOS)

- ✓ **Overcome Disease Heterogeneity**
- ✓ **Stronger KIT inhibition**

RIPRETINIB (DCC-2618): Phase I trial activity

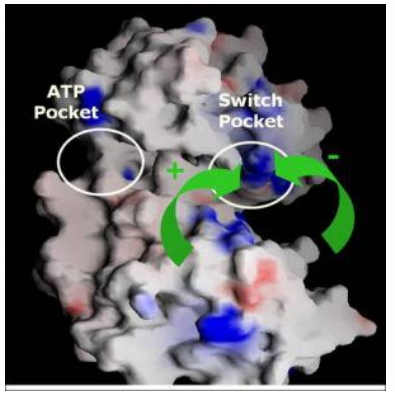


PD=Progressive Disease. SD=Stable Disease. PR=Partial Response.
* indicates patients not dosed at 150mg QD # PDGFRA mutation

BEST RESPONSE:

2nd and 3rd line

Pts at > 100mg/d (n=54)



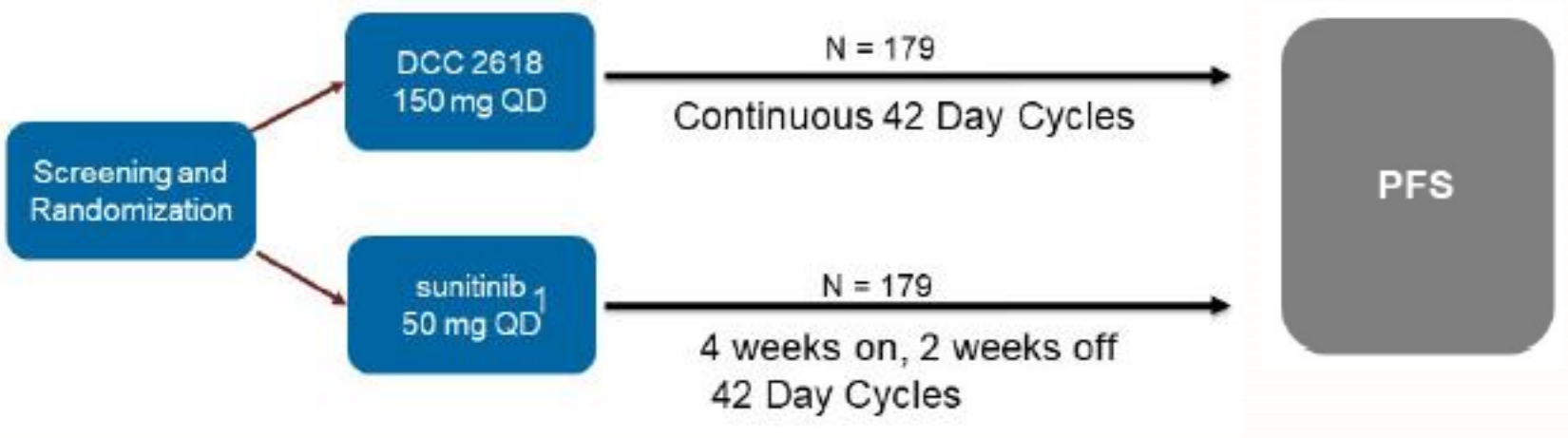
George et al, ASCO 2018

RIPRETINIB (DCC-2618)studies

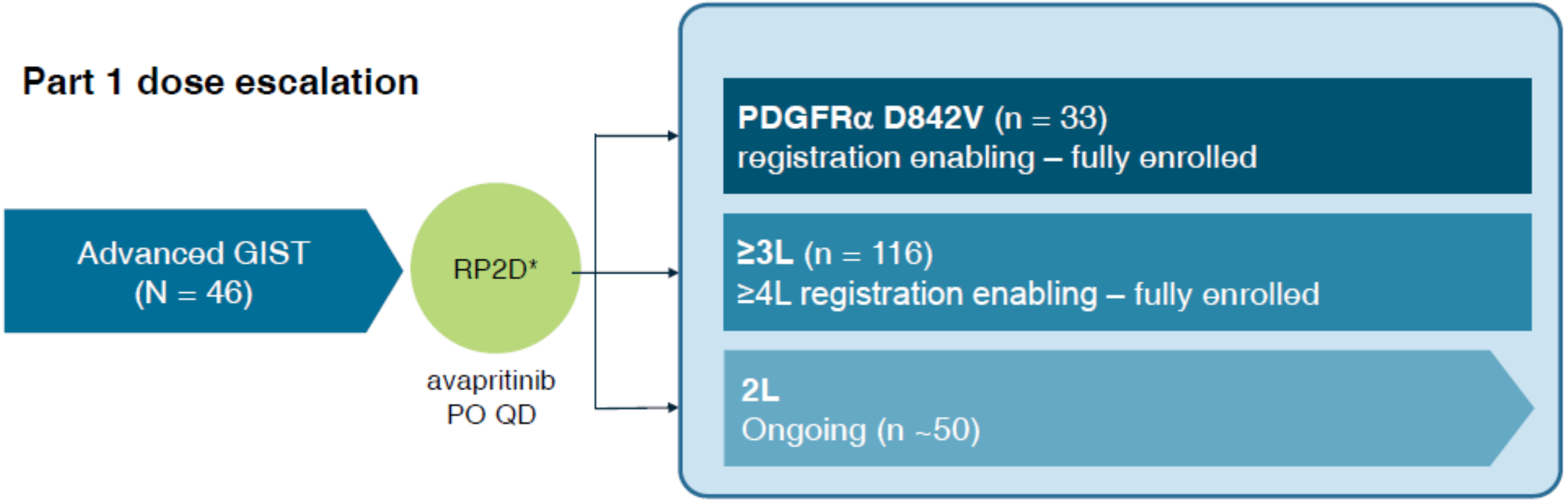
invictus

A Phase 3, **IN**ter**V**entional, Double-Blind Study to Assess Safety and Efficacy of DCC-2618 **I**n Patients with Advanced **c**-KIT/PDGFRA Gastrointestinal Stromal **TU**mor**S** Who Have Received Prior Treatment with Imatinib, Sunitinib, and Regorafenib

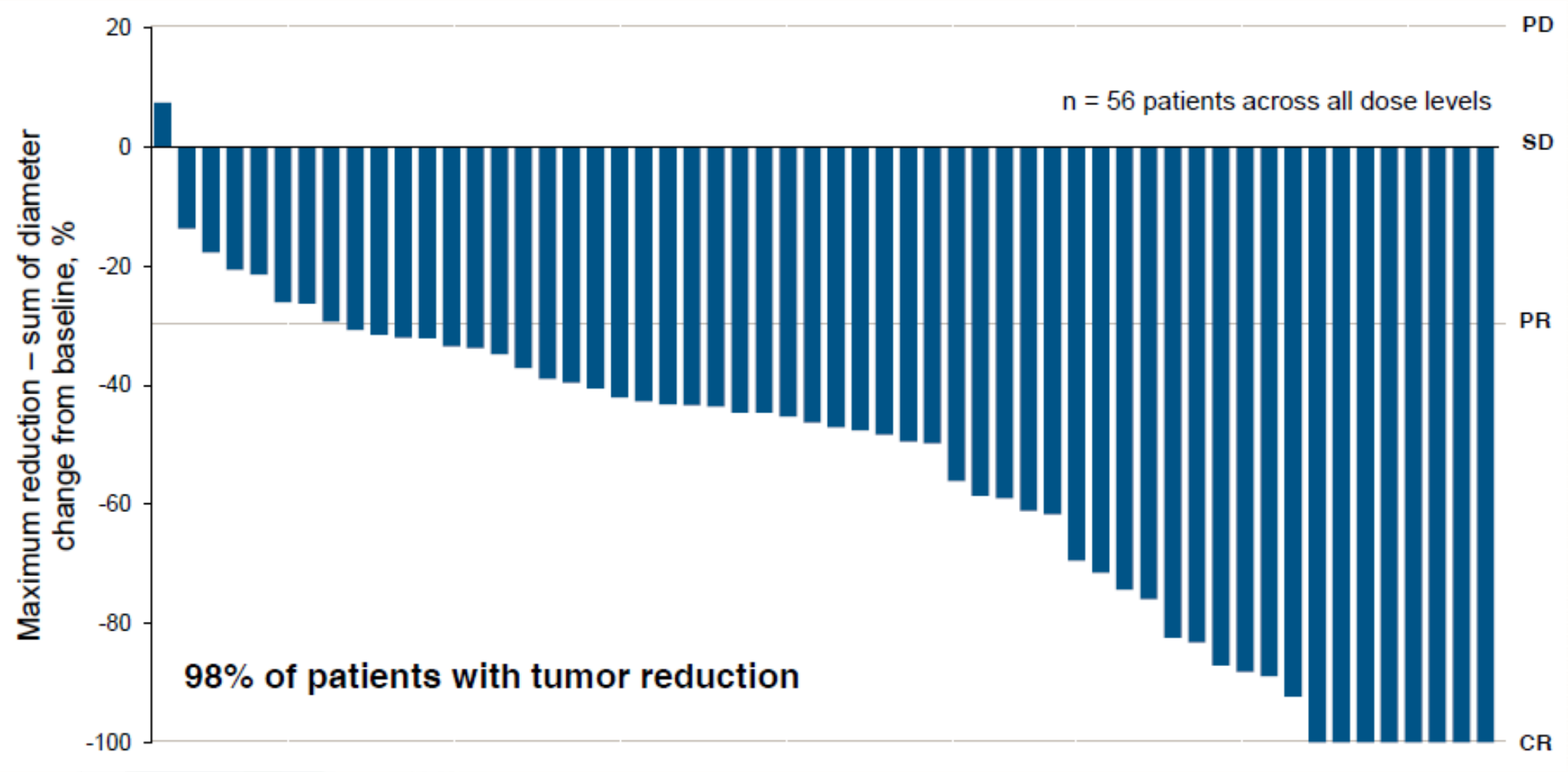
INTRIGUE



AVAPRITINIB (BLU-285) – phase I navigator study design



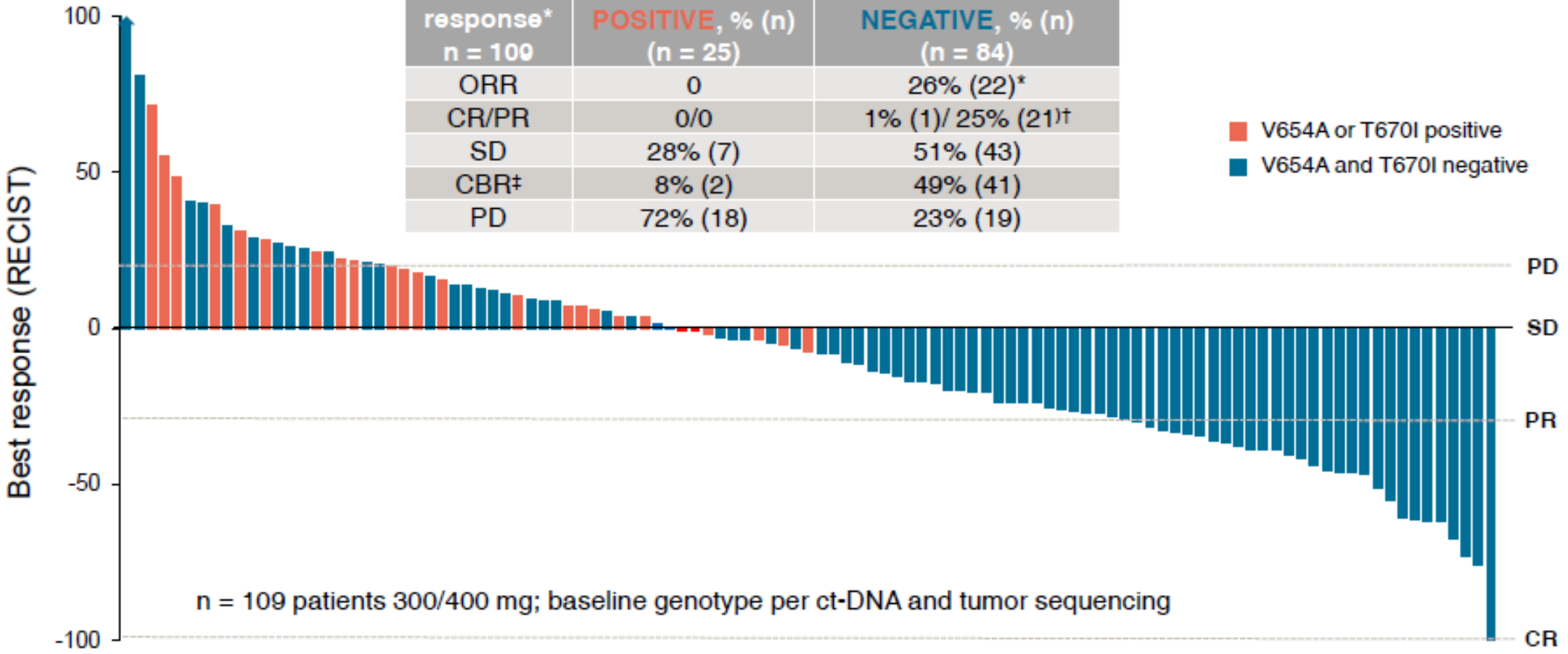
AVAPRITINIB (BLU-285) – phase I navigator study
PDGFRA d842v-mutant gist



Heinrich et al, CTOS 2018

AVAPRITINIB (BLU-285) – phase I navigator study kit-mutant gist ≥ 4L

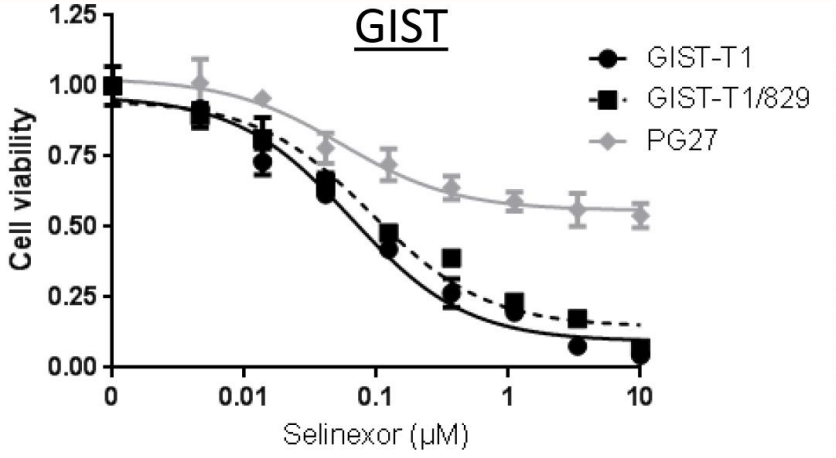
Best response* n = 109	V654A or T670I POSITIVE, % (n) (n = 25)	V654A and T670I NEGATIVE, % (n) (n = 84)
ORR	0	26% (22)*
CR/PR	0/0	1% (1)/ 25% (21)†
SD	28% (7)	51% (43)
CBR‡	8% (2)	49% (41)
PD	72% (18)	23% (19)

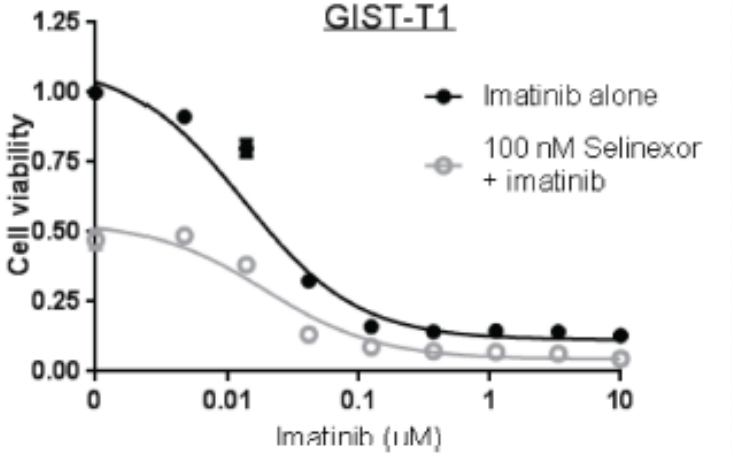


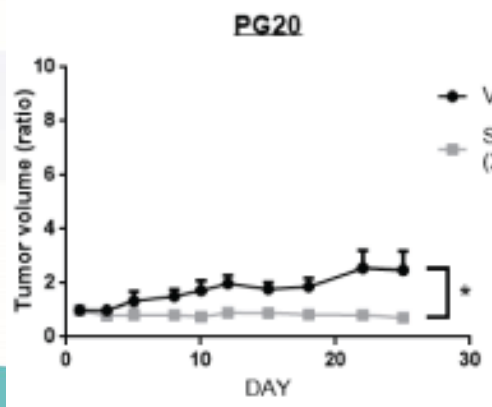
Heinrich et al, CTOS 2018

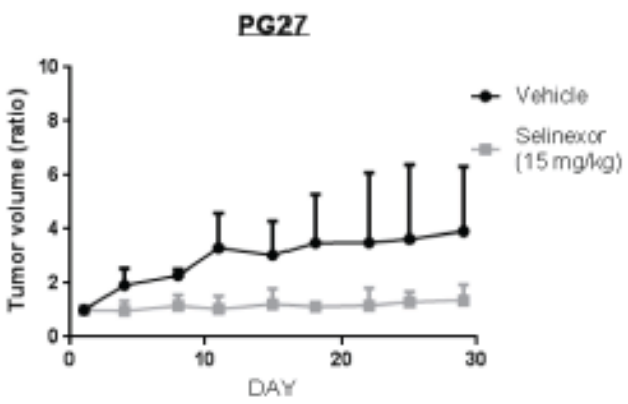
OTHER THERAPEUTIC STRATEGIES
SELIGIST: IMATINIB + SELINEXOR

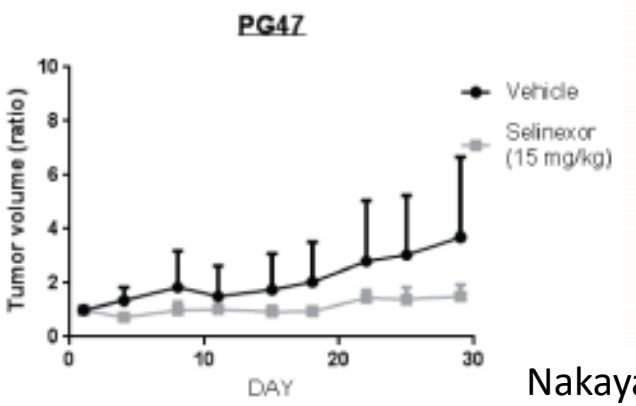
Selinexor: XPO1 inhibitor







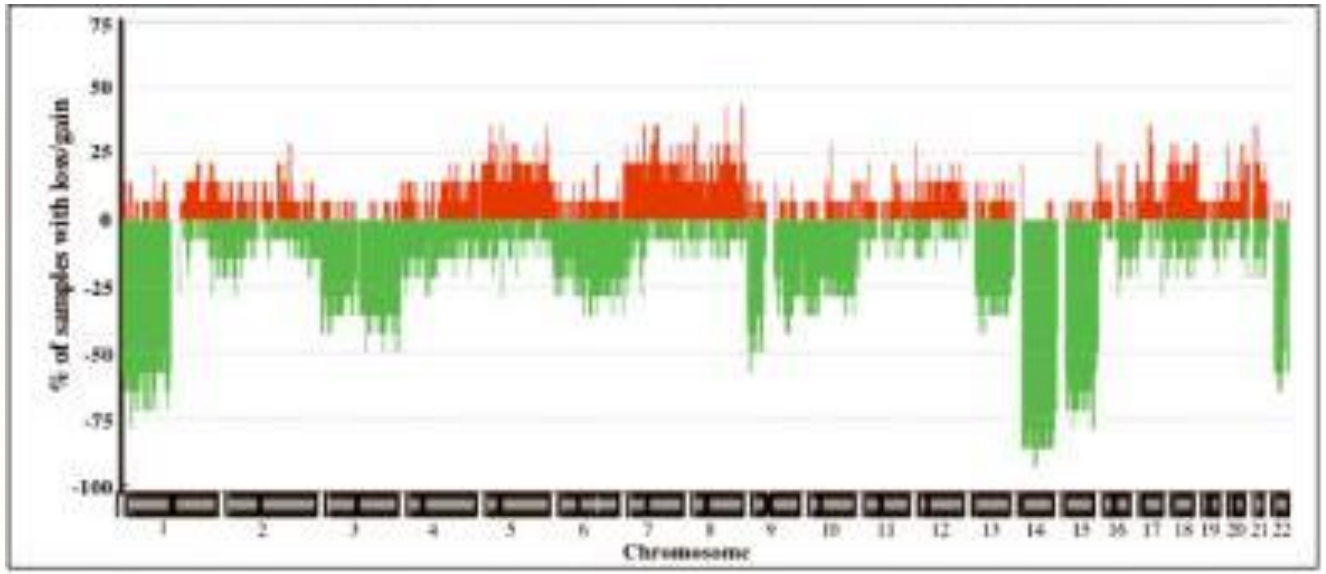




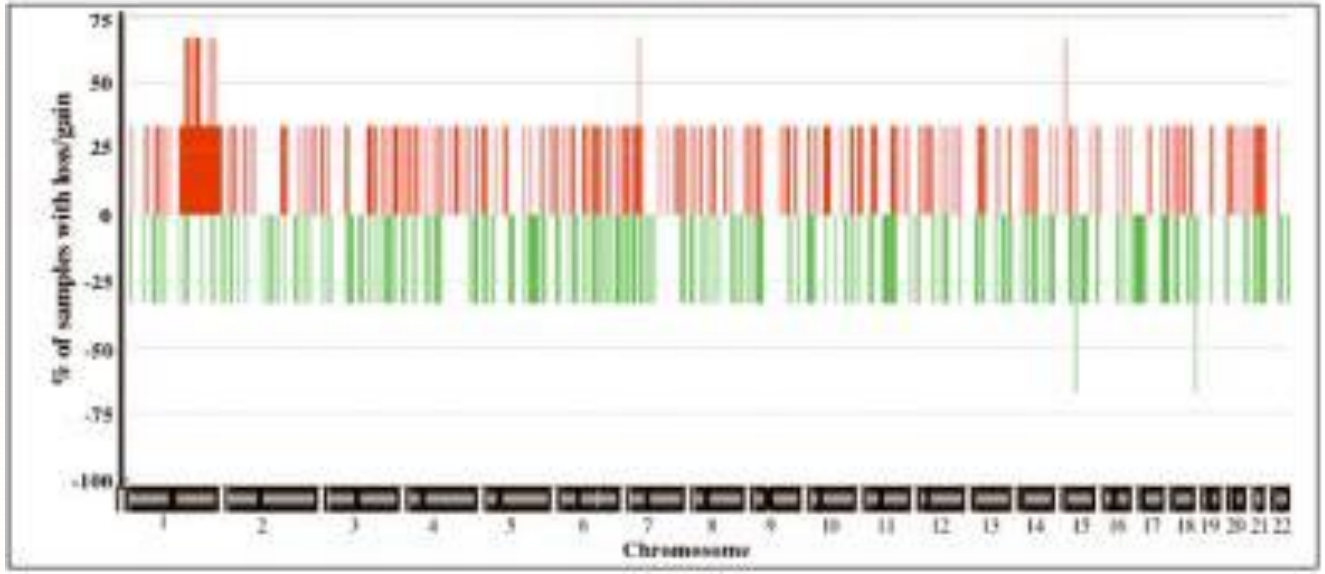
Nakayama et al. Oncotarget 2015

CYTOGENETIC MAP OF *KIT/PDGFRa* MUTATED AND WT GIST

KIT-PDGFRa MUTATED GIST

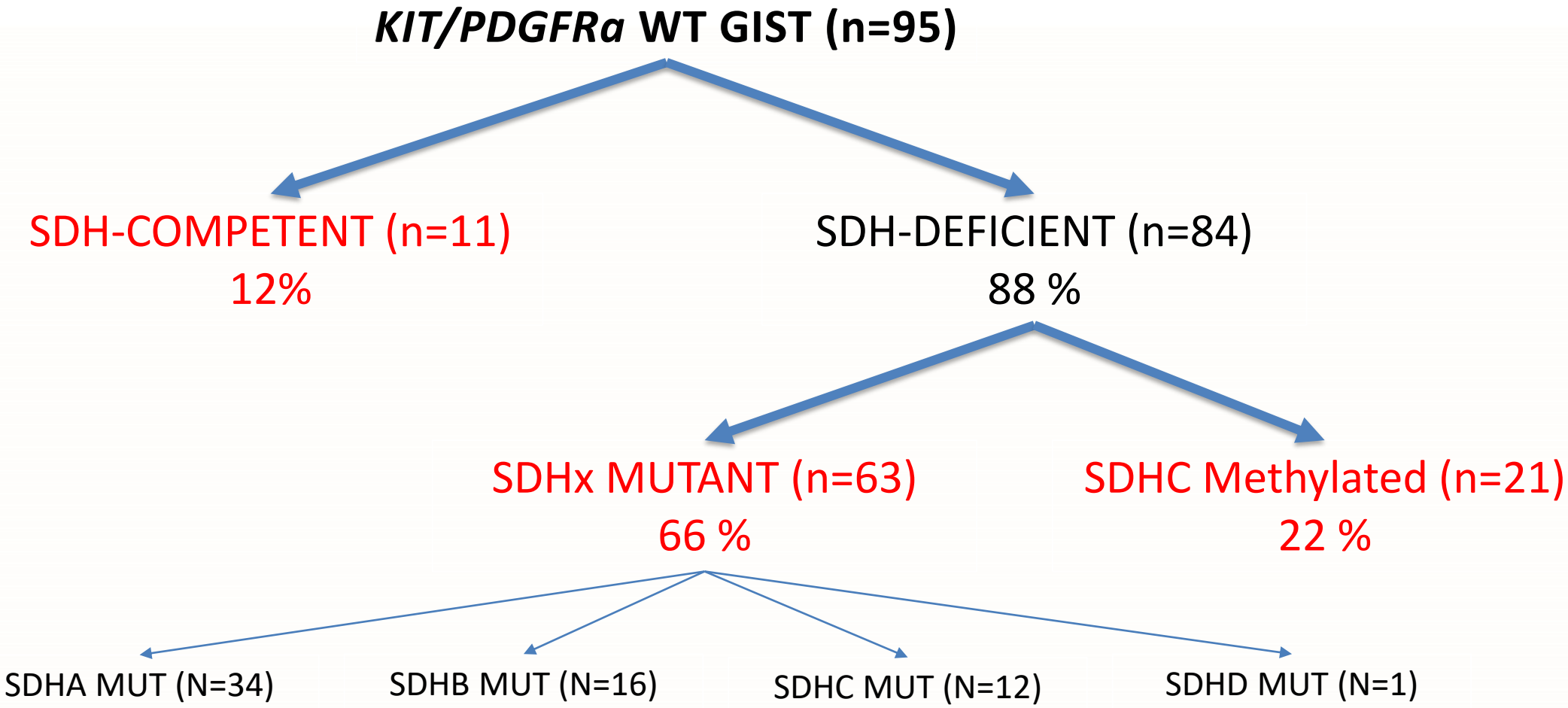


KIT-PDGFRa WILD TYPE GIST



M Belinsky, Genes Chromosomes Cancer.48, 2009.

Molecular Subtypes of *KIT/PDGFRa* WT GIST



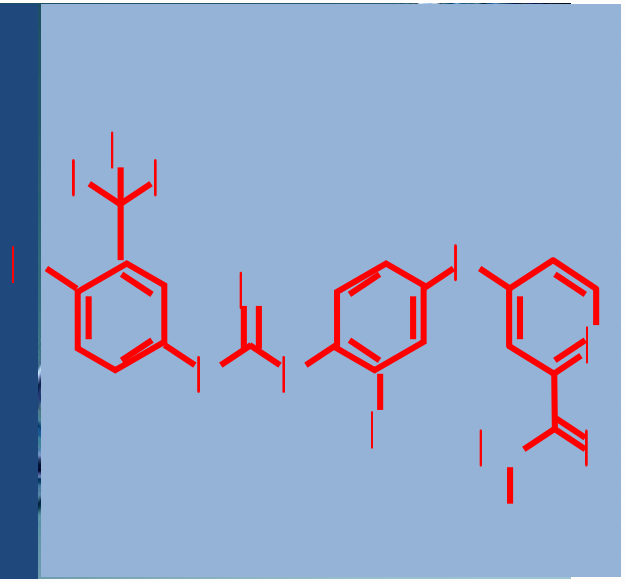
S Boikos, JAMA Oncol. 2016 July 01; 2(7): 922–928 .

OTHER THERAPEUTIC STRATEGIES
REGISTRI: Regorafenib in WT GIST

REGORAFENIB in WT GIST

- **GEIS 40**

REGISTRI (REgorafenib GIST TRIal)



KIT, RET, RAF-1, BRAF, and BRAFV600E; VEGFR1-3, TIE2; PDGFR-b, FGFR

REMARKS

- GIST represents a model of MOLECULAR TARGETED THERAPY in solid tumors with 3 already approved drugs
- The treatment of GIST demands high qualification, team work and innovative approaches
- *KIT/PDGFR* WT GIST requires a specific research way
- RIPRETINIB and AVAPRITINIB represent the PROMISING upcoming future in advanced GIST
- Clinical Trials are the way to IMPROVE OUTCOME in GIST

THANK-YOU

jmartin@mustbesevilla.org