clinical practice guidelines

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Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

Identification of KIT Gain-of-Function Mutations

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

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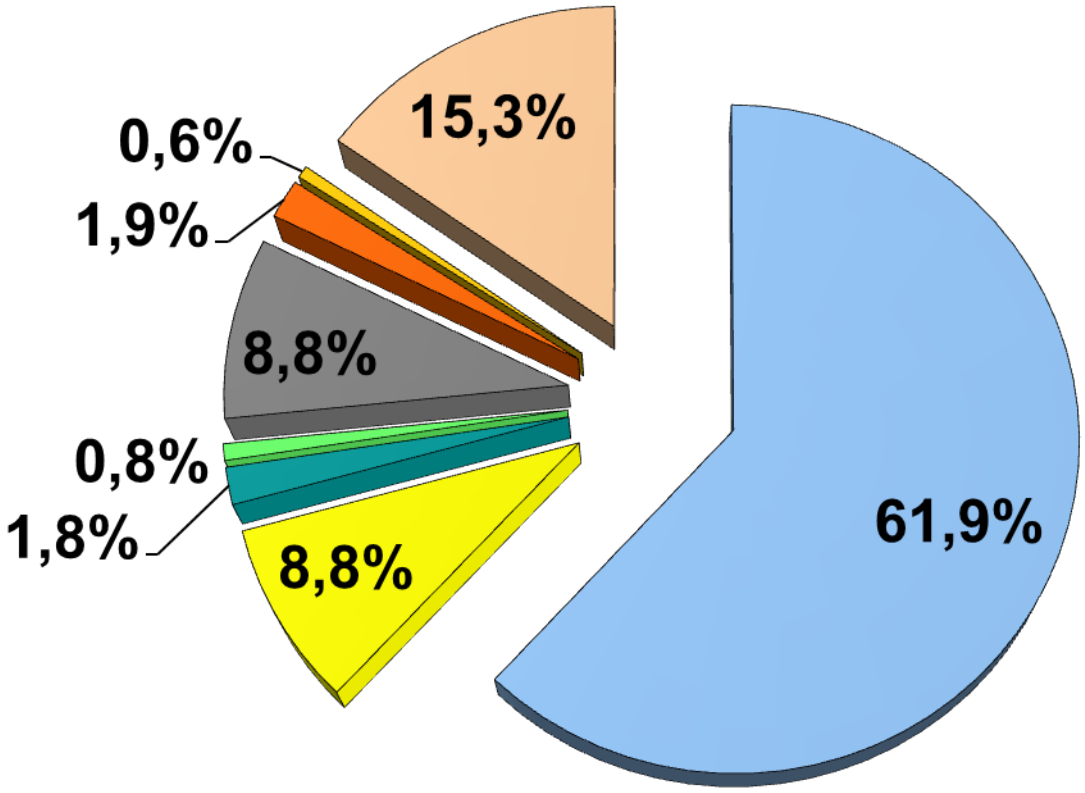
Science 279:577-580, 1998

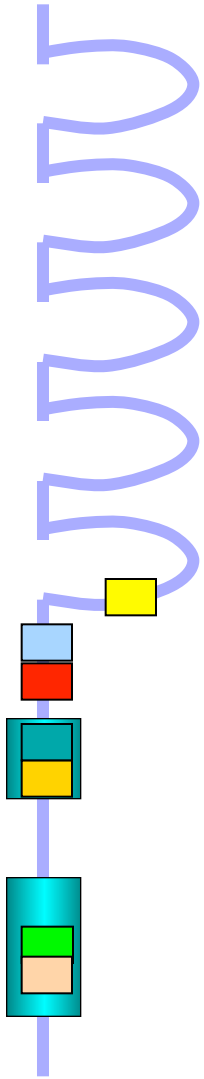
- KIT staining was positive in 46 of 49 GIST (94%)
- 5 of 6 GIST had mutations in KIT gene
- Mutant forms of KIT are constitutively active

Frequenz und Lokalisation von *KIT*- und *PDGFRA*-Mutationen



GSRCB* (n=1231)

- KIT exon 11
- KIT exon 9
- KIT exon 13
- KIT exon 17
- wild type
- PDGFRA exon 12
- PDGFRA exon 14
- PDGFRA exon 18

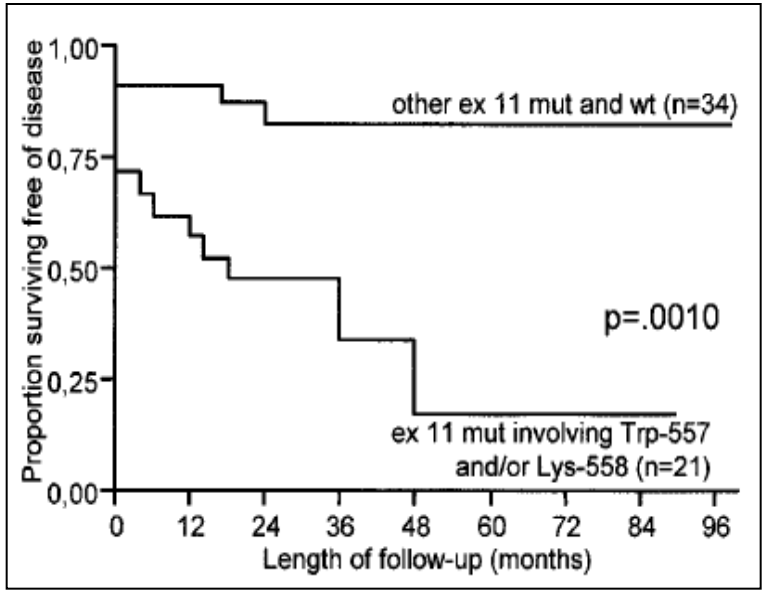


*GSRCB = GIST and Sarcoma Registry Cologne/Bonn

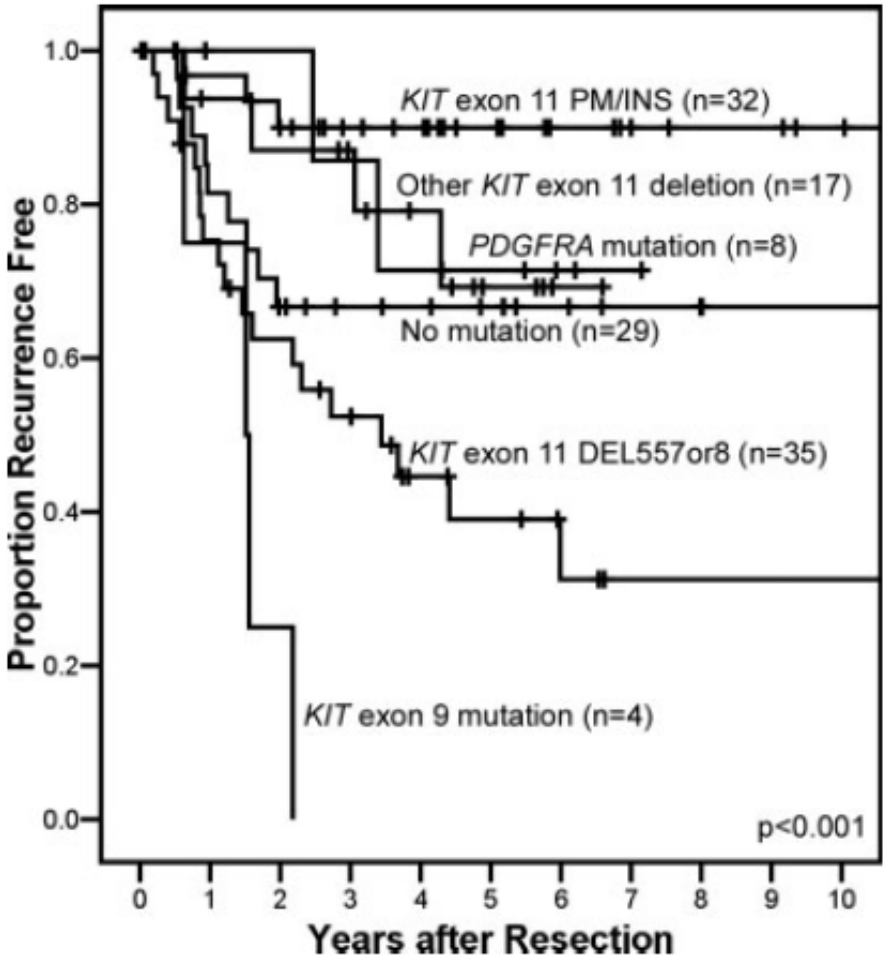
Prognostic influence of mutational status

- Some *KIT* exon 11 mutations (e.g. del 557-558)
- *KIT* exon 9 mutation
- *PDGFR* mutations
- *KIT / PDGFR* wild type

Negative Prognostic Impact of *KIT* Exon 11 Mutations



Wardelmann et al. Int J Cancer 2003;106(6):887-895.



Dematteo et al. Cancer 2008; 112(3):608–615.

Predictive influence of mutational status

- *KIT* exon 11 mutation
- *KIT* exon 9 mutation
- Some *PDGFR* exon 18 mutations (e.g. D842V)
- *KIT / PDGFR* wild type

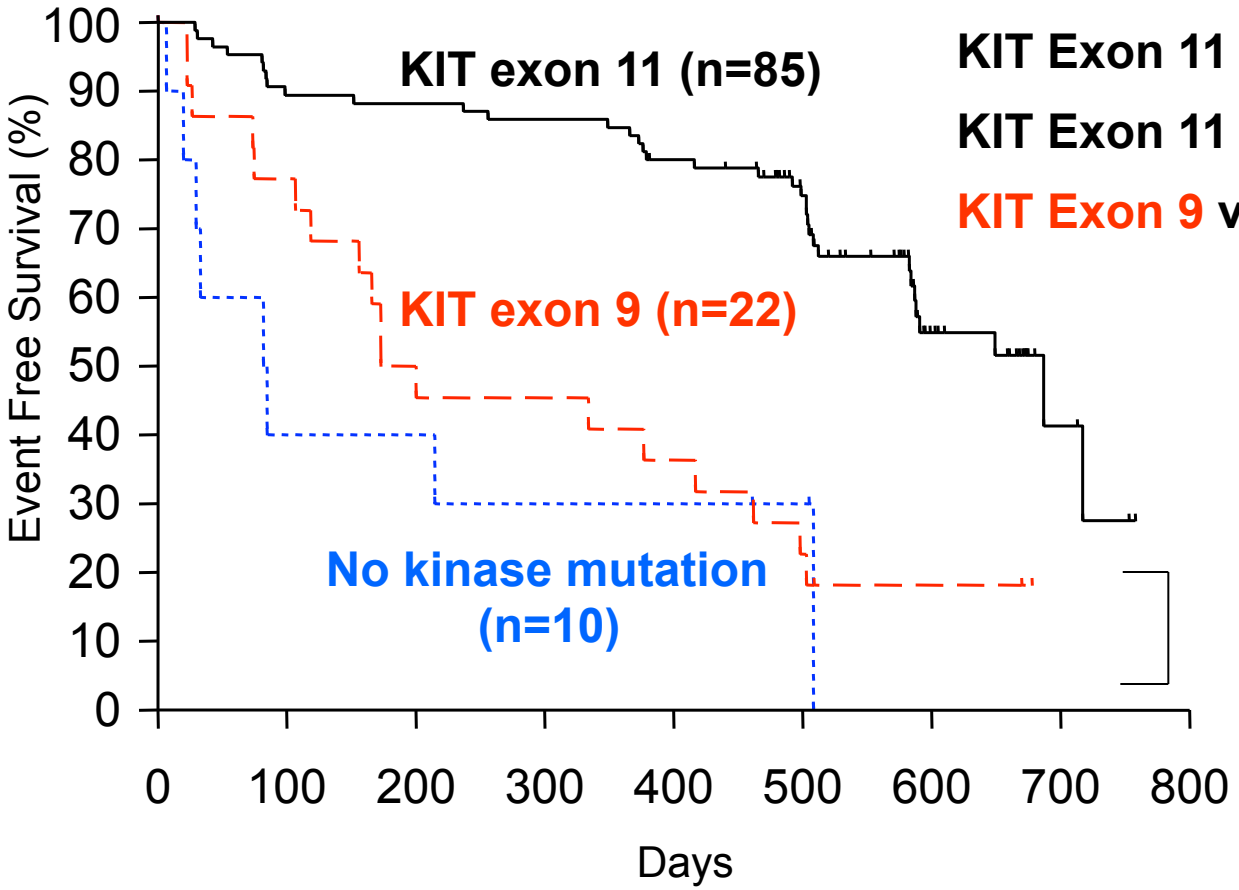
Functional Resistance: Phase III data

Response	KIT mutants				PDGFRA mutants	Wild type	Total
	Exon 9	Exon 11	Exon 13	Exon 17			
CR	3 5.17%	16 6.45%	0 -	0 -	0 -	0 -	19 5.04%
PR	17 29.31%	152 61.29%	4 66.67%	2 66.67%	3 30.00%	12 23.08%	190 50.40%
NC	27 46.55%	63 25.40%	2 33.33%	1 33.33%	3 30.00%	26 50.00%	122 32.36%
PD	10 17.24%	8 3.23%	0 -	0 -	4 40.00%	10 19.23%	32 8.49%
Uneval.	1 1.72%	9 3.63%	0 -	0 -	0 -	4 7.69%	14 3.71%
Total	58	248	6	3	10	52	377

CR, complete Remission; PR, partial response; NC, stable disease; PD, progressive disease; Uneval., not evaluated (all according to RECIST criteria)

Debiec-Rychter et al. Eur J Cancer. 2006;42:1093.

KIT and PDGFRα Mutations Predict Event Free Survival on Imatinib



KIT Exon 11 vs. Exon 9 p<0.0001

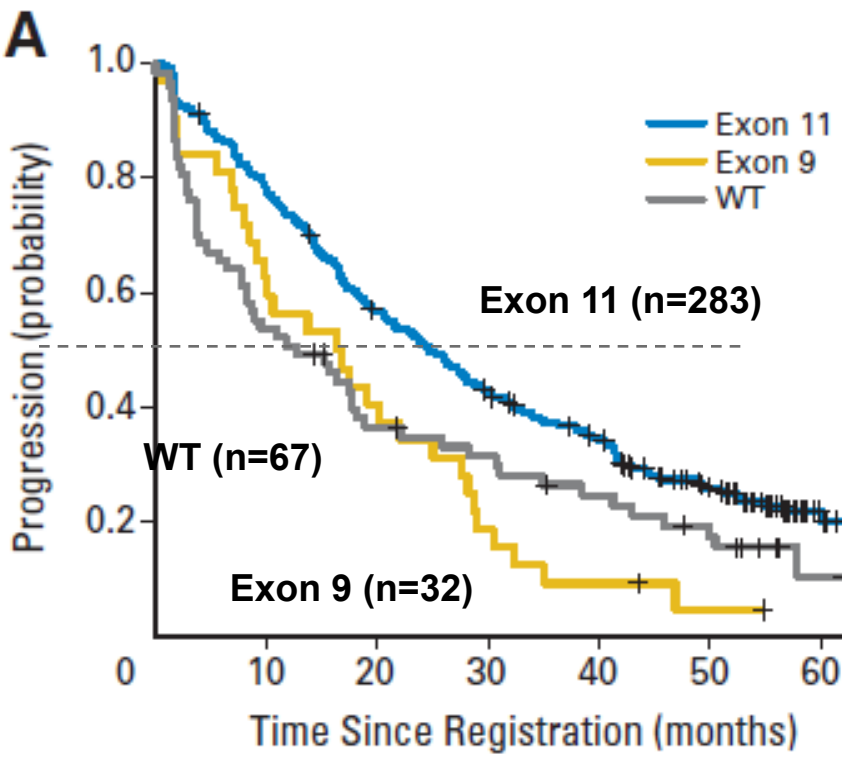
KIT Exon 11 vs. None p<0.0001

KIT Exon 9 vs. None p=0.52

Heinrich et al. J Clin Oncol. 2003;21(23):4342-4349.

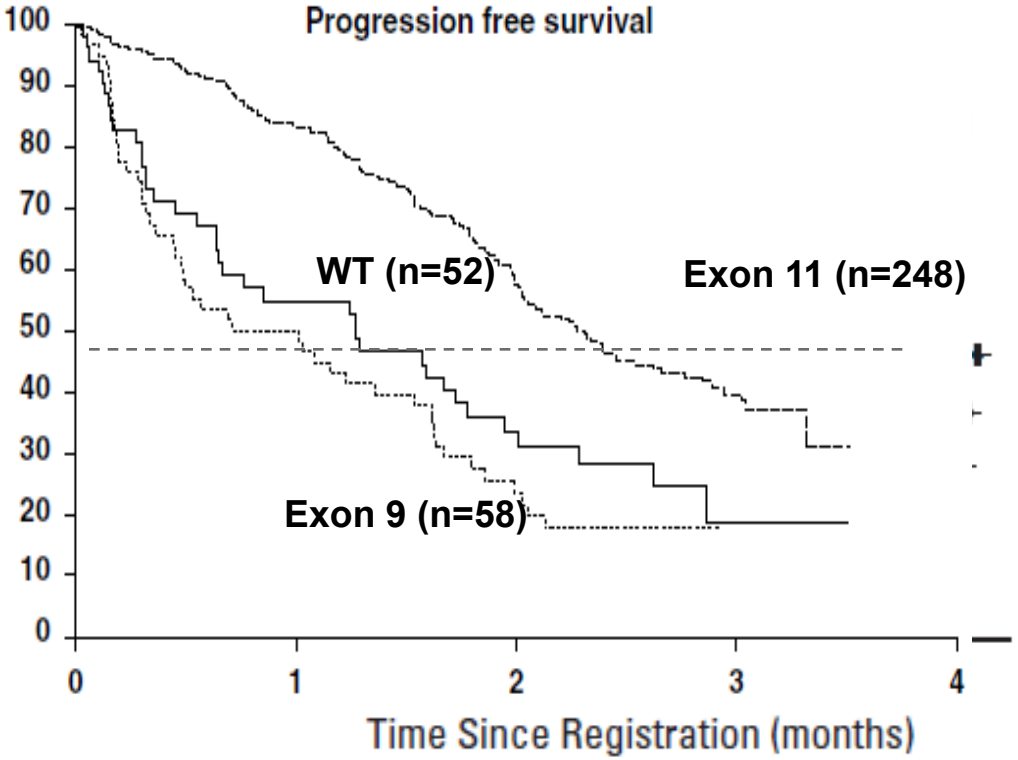
Phase III Trials: Genotype vs Progression-Free Survival (All Doses)

SWOG S0033



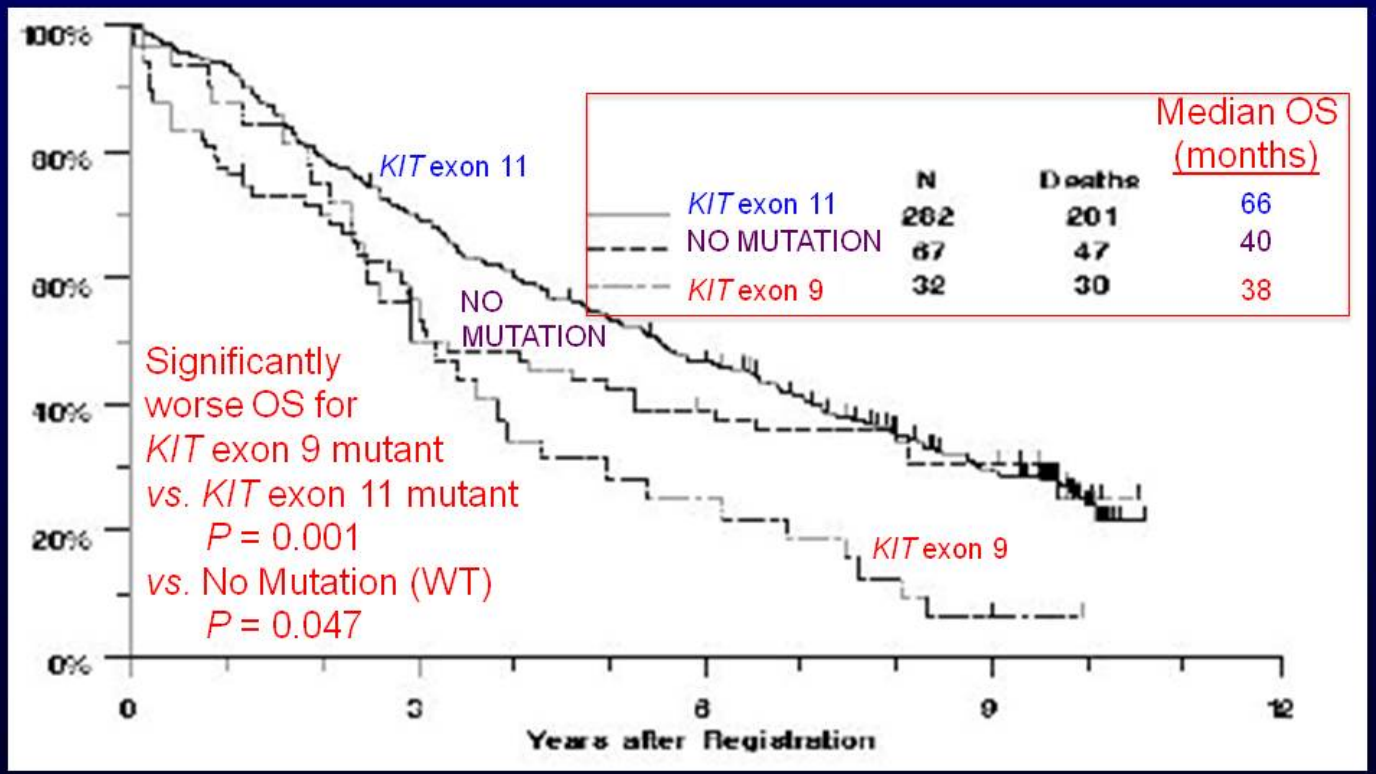
Heinrich et al. J Clin Onc 2008, 26(33):5360-7

EORTC/ISG/AGITG



Debiec-Rychter et al. Eur J Cancer 2006, 42(8):1093-103

S0033 Overall Survival by GIST Genotype – 2014 data



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Progression-Free Survival according to muational status

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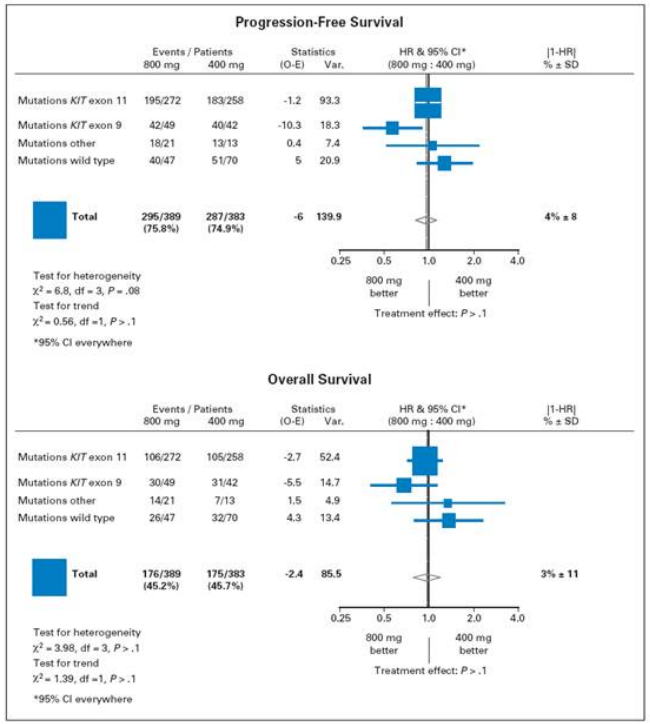
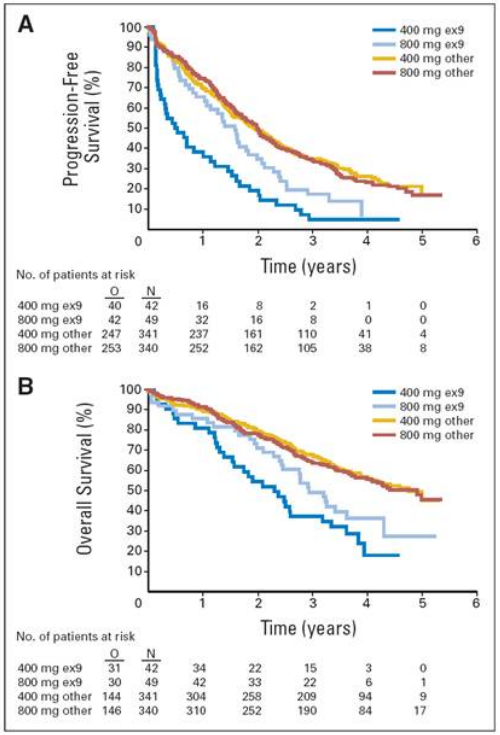
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Two Doses of Imatinib for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumors: A Meta-Analysis of 1,640 Patients

Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST)

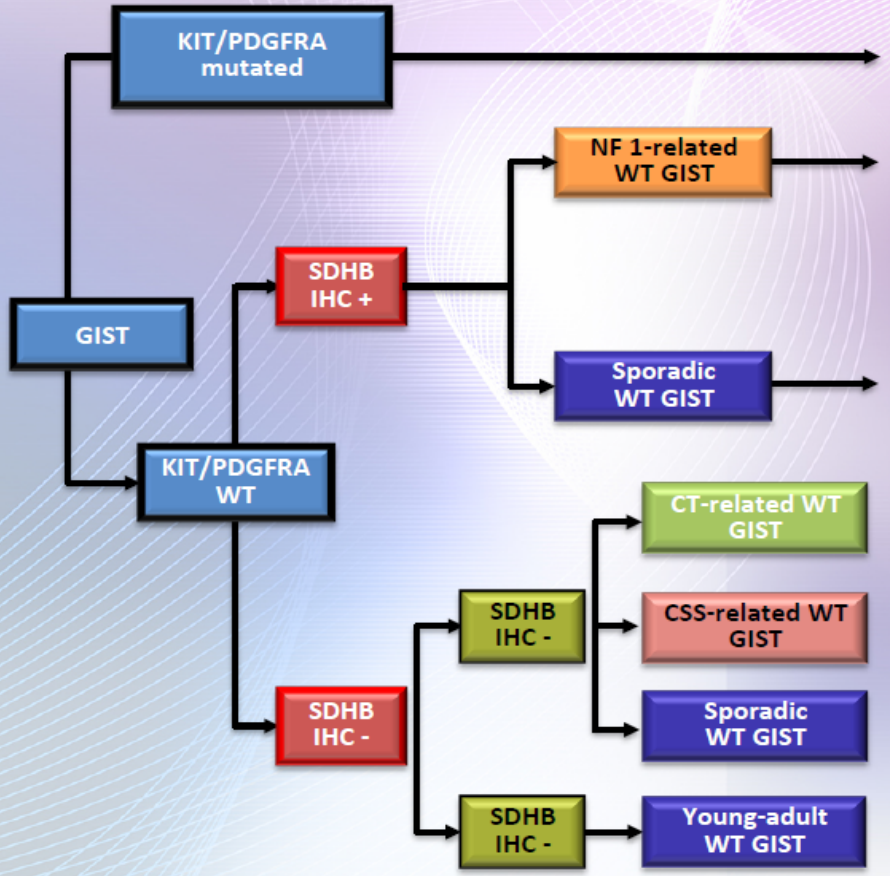




Wild-Type GIST
(No KIT or PDGFRA Mutation)

WT GIST

- SDH Deficient GIST
  - Paediatric GIST
  - Carney Triad:
    - "Leiomyosarcoma"/GIST
    - Pulmonary chondroma
    - Paraganglioma
  - Carney-Stratakis Syndrome
    - GIST
    - Paraganglioma
- NF-1
- Non-Syndromic WT GIST



Nannini M, et al. *J Med Genet.* 2013;50(10):653-61.

Wild-Type GIST (No KIT or PDGFRA Mutation)

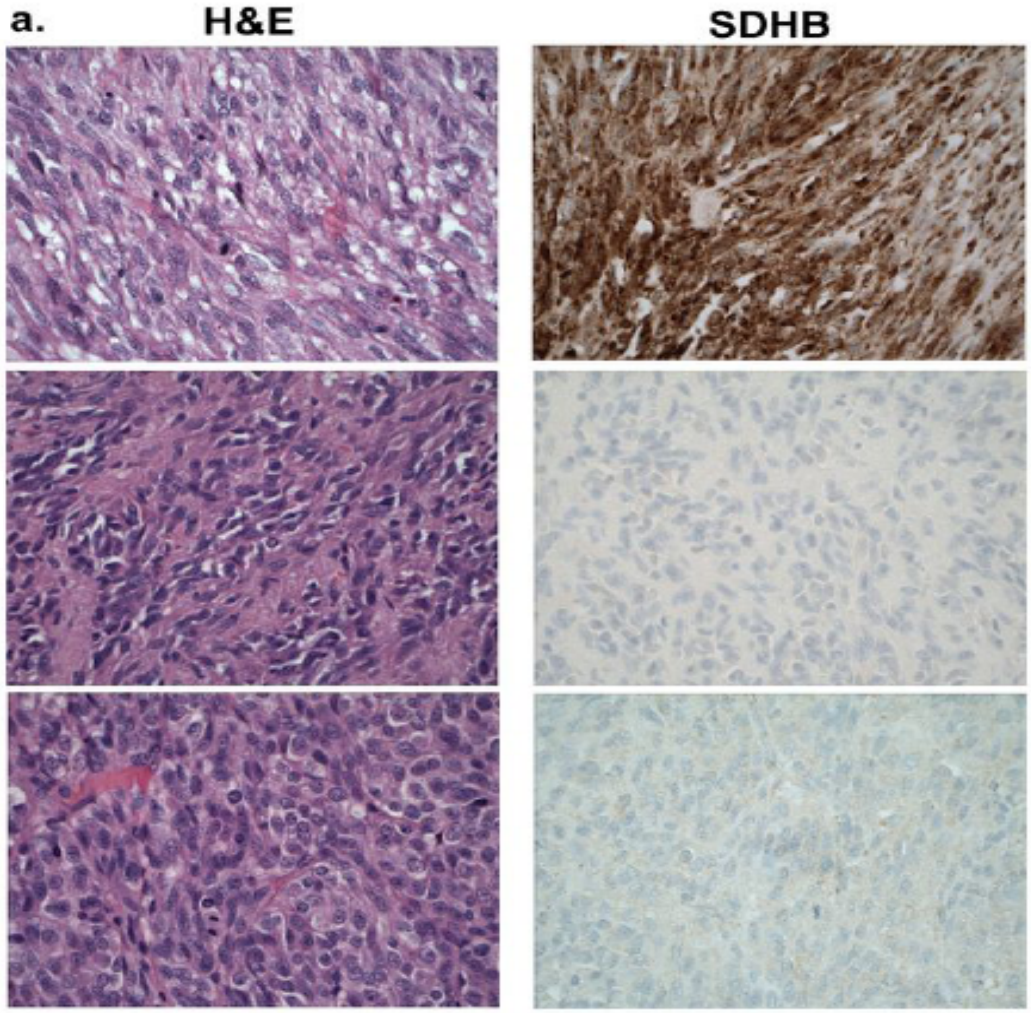
Alteration	Syndrome	Estimated Frequency	References
Germline NF1 mutation	NF type 1	Rare	Andersson et al. *Am J Surg Pathol*. 2005; 29:1170-1176
BRAF mutation		< 7%	Agaram et al. *Genes Chromosomes Cancer*. 2008;47(10):853-859 Agaimy et al. J Clin Pathol 2009;62:613–6.
KRAS or NRAS mutation		<1%	Heinrich and Corless, unpublished
Increased IGF1R expression		~50%	Tarn et al. *PNAS*. 2008;105(24):8387-8392
Germline SDHA, SDHB, SDHC or SDHD mutation	Carney-Stratakis	~12%	Janeway et al. *PNAS*. 2011;108(1):314-318 Pantaleo et al. J Natl Cancer Inst. 2011;103(12):983-7
Loss of SDHB expression (probably post-transcriptional)	(Carney triad)	~30%	Janeway et al. *PNAS*. 2011;108(1):314-318

SDHB Immunohistochemistry

KIT-mutant

SDH-mutant

‘Wild-type’



Janeway et al. PNAS 2011;108(1):314-8

Molecular classification of GIST

Genetic type	Relative frequency	Anatomic distribution	Germline examples
KIT mutation (relative frequency 75–80%)			
Exon 8	Rare	Small bowel	One kindred
Exon 9 insertion AY502-503	10%	Small bowel and colon	None
Exon 11 (deletions, single nucleotide substitutions and insertions)	67%	All sites	Several kindreds
Exon 13 K642E	1%	All sites	Two kindreds
Exon 17 D820Y, N822K and Y823D	1%	All sites	Five kindreds
PDGFRA mutation (relative frequency 5–8%)			
Exon 12 (such as V561D)	1%	All sites	Two kindreds
Exon 14 N659K	<1%	Stomach	None
Exon 18 D842V	5%	Stomach, mesentery and omentum	None
Exon 18 (such as deletion of amino acids IMHD 842–846)	1%	All sites	One kindred
KIT and PDGFRA wild-type (relative frequency 12–15%)			
BRAF V600E	~7–15%		
SDHA, *SDHB*, *SDHC* and *SDHD* mutations	~2%	Stomach and small bowel	Carney–Stratakis
HRAS and *NRAS* mutation	<1%		
Sporadic paediatric GISTs	~1%	Stomach	Not heritable
GISTs as part of the Carney triad	~1%	Stomach	Not heritable
NF1-related	Rare	Small bowel	Numerous

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type I; *PDGFRA*, platelet-derived growth factor receptor-α; SDH, succinate dehydrogenase.

Corless C. et al Nature Reviews 2011, 11:865

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Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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area). Mutational analysis for known mutations involving *KIT* and PDGFRA genes can confirm the diagnosis of GIST, if doubtful (particularly in CD117/DOG1-negative suspect GIST). Mutational analysis has a predictive value for sensitivity to molecular-targeted therapy, and prognostic value, so that its inclusion in the diagnostic work-up of all GISTs should be considered standard practice (with the possible exclusion of <2 cm non-rectal GISTs, which are very unlikely ever to be candidates for medical treatment). Centralisation of mutational analysis in a laboratory enrolled in an external quality assurance programme and with expertise in the disease may be useful. In *KIT*/PDGFRA wild type (WT) GIST, immunohistochemistry for SDHB is done. The diagnosis should be made or confirmed by an expert pathologist at a reference centre. The collection of fresh/frozen tissue is encouraged, because

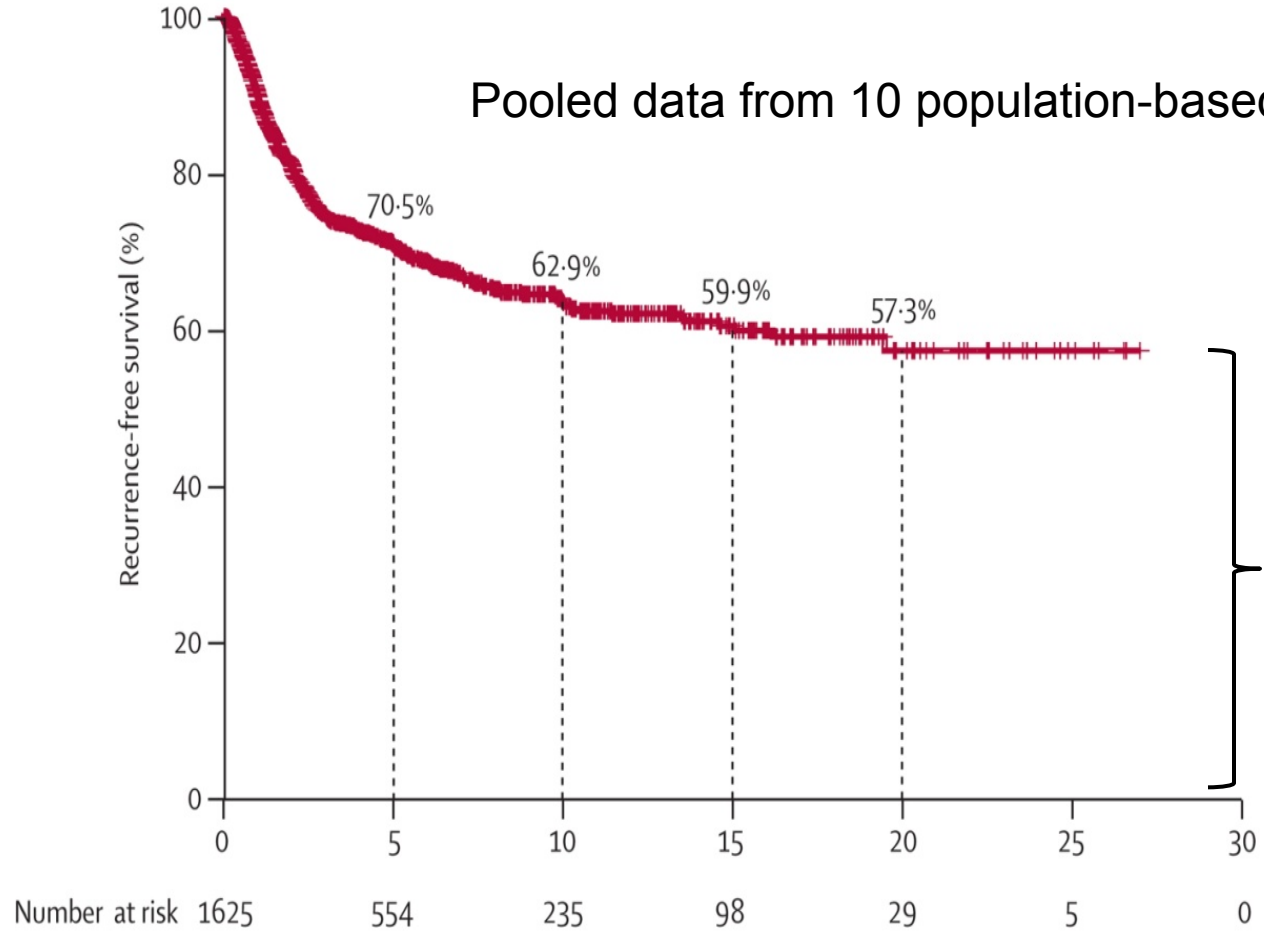
HELIOS Kliniken
Jeder Moment ist Medizin

GISTumoren adjuvant therapieren?

Peter Reichardt

HELIOS Klinikum Berlin-Buch / Interdisziplinäre Onkologie / Sarkomzentrum Berlin-Brandenburg

Risk of recurrence after surgey alone



Joensuu et al. Lancet Oncol 2012; 13:265-74

Frequently used risk stratification schemes

Tumor variable	NIH[1]	AFIP[2]	Modified NIH[3]
Mitotic count categories (/ 50 HPFs)	5/50 10/50	5/50	5/50 10/50
Size categories	2 cm 5 cm 10 cm	2 cm 5 cm 10 cm	2 cm 5 cm 10 cm
Site categories	0	4	2
Tumor rupture categories	0	0	yes / no

[1]*Fletcher et al. Hum Pathol 2002; 33:459-65*
[2]*Miettinen & Lasota, Semin Diagn Pathol 2006; 23:70-83*
[3]*Joensuu, Hum Pathol 2008; 39:1411-9*

AFIP Risk Group Classification

Group	Group definition	Patients with progressive disease during long-term follow-up			
		Gastric %	Jejunal %	Duodenal %	Rectal %
1	≤2.0 cm, ≤5/50 HPF	0	0	0	0
2	2.1-5.0 cm, ≤5/50 HPF	1.9	4.3	8.3	8.5
3a	5.1-10.0 cm, ≤5/50 HPF	3.6	24		
3b	>10.0 cm, ≤5/50 HPF	12	52	34*	57*
4	≤2.0 cm, >5/50 HPF	0*	50*	-	54
5	2.1-5.0 cm, >5/50 HPF	16	73	50	52
6a	5.1-10.0 cm, >5/50 HPF	55	85		
6b	>10.0 cm >5/50 HPF	86	90	86*	71*

*very low numbers

Miettinen M, Lasota J., Sem Diagn Pathol 2006;23:70-83

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4	≤2.0 cm, >5/50 HPF	0*	50*	-	54
5	2.1-5.0 cm, >5/50 HPF	16	73	50	52
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4	≤2.0 cm, >5/50 HPF	0*	50*	-	54
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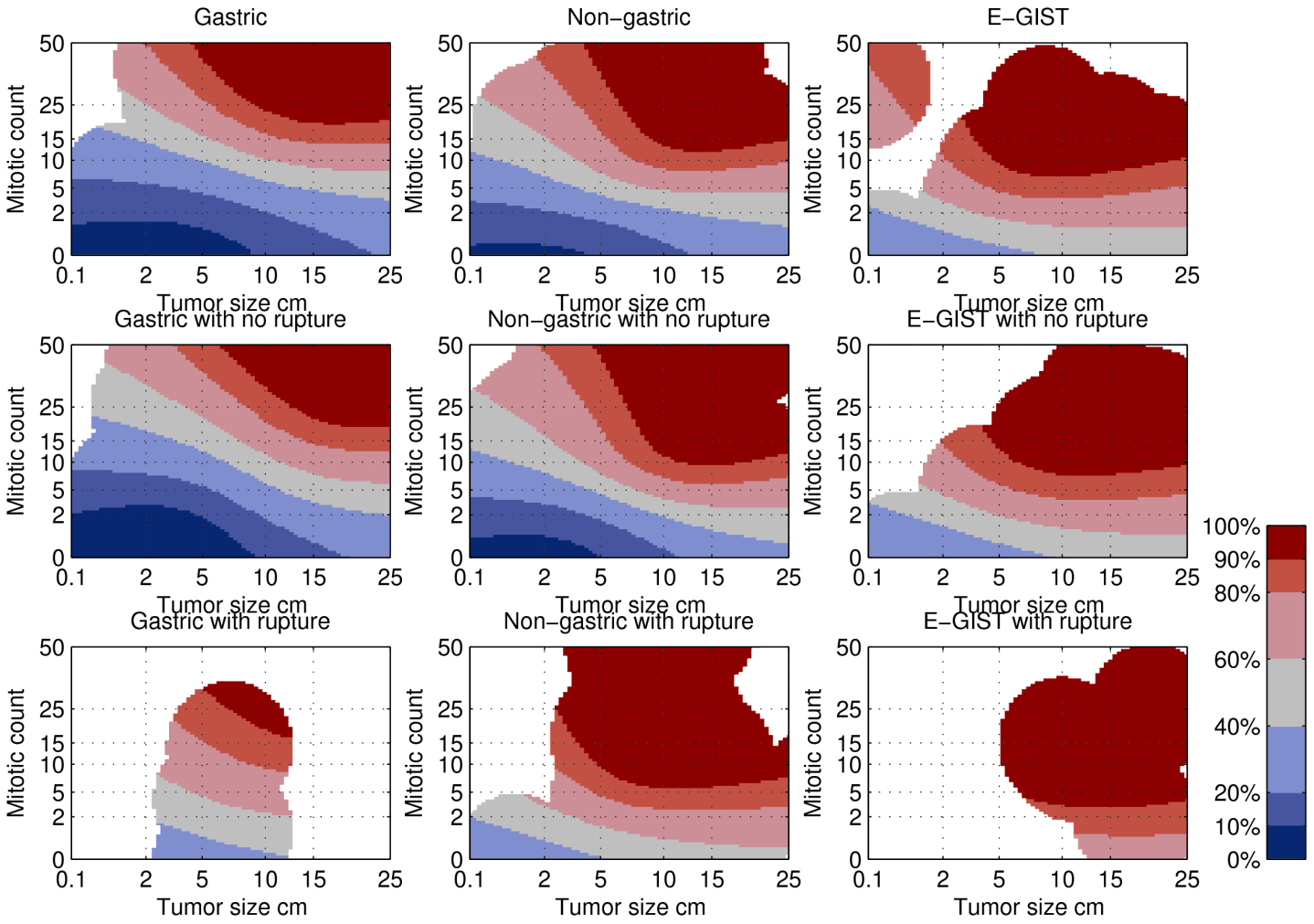
Miettinen M, Lasota J., Sem Diagn Pathol 2006;23:70-83

Prognostic contour maps, 10-year RFS

Rupture ?

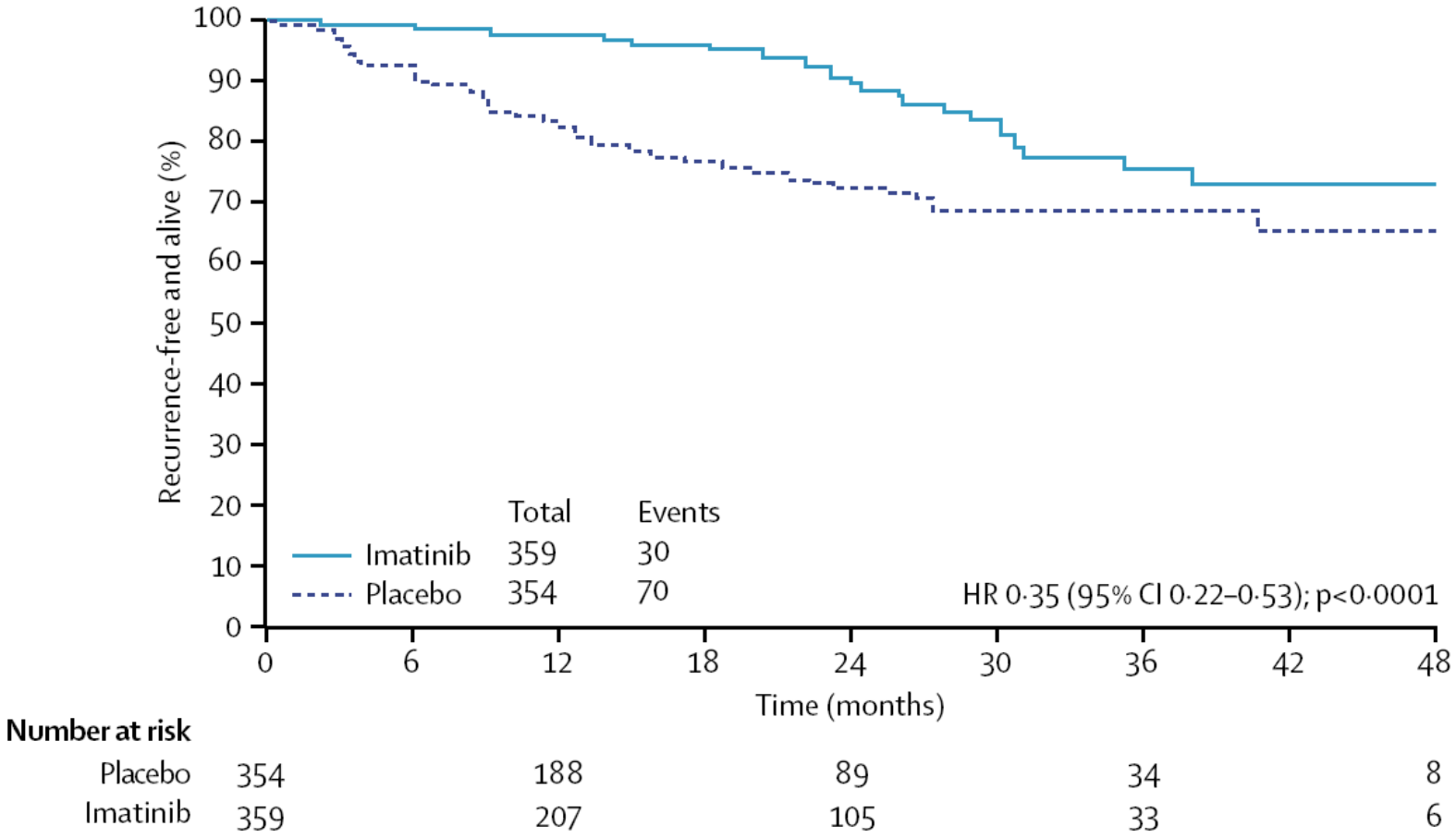
No rupture

Rupture present



Joensuu et al. Lancet Oncol 2012; 13:265-74

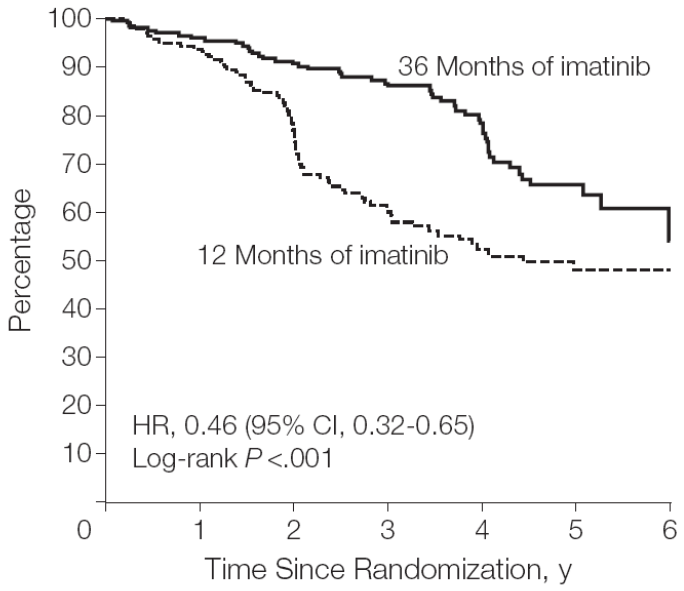
Z9001: Recurrence-Free Survival



DeMatteo et al. Lancet. 2009;373:1097-1104.

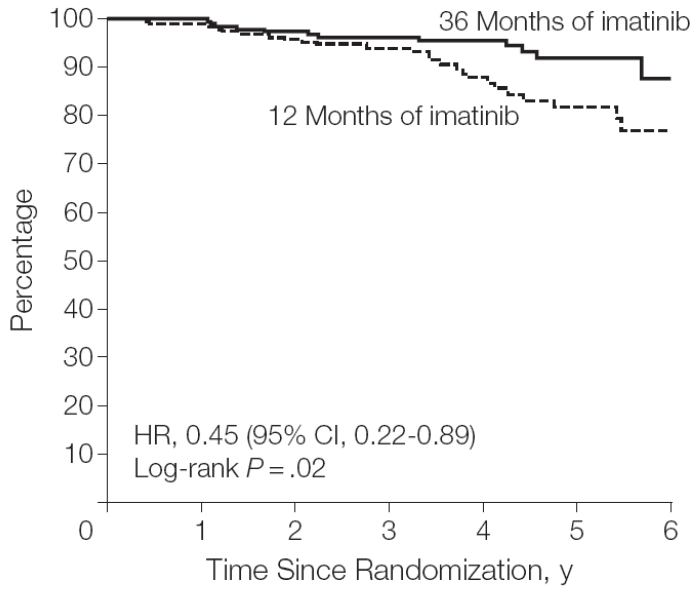
SSGXVIII/AIO: RFS and OS

A Recurrence-free survival: intention-to-treat population



No. of patients							
36 Months of imatinib	198	184	173	133	82	39	8
12 Months of imatinib	199	177	137	88	49	27	10

C Overall survival: intention-to-treat population

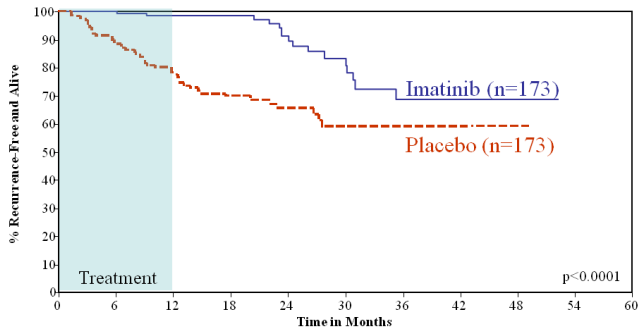


No. of patients							
36 Months of imatinib	198	192	184	152	100	56	13
12 Months of imatinib	199	188	176	140	87	46	20

Joensuu, ..., Reichardt et al., JAMA 307:1265-1272, 2012

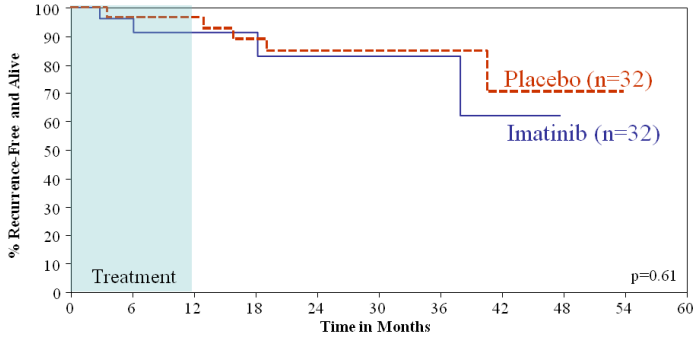
Influence of mutational status on outcome of adjuvant imatinib

RFS for Exon 11

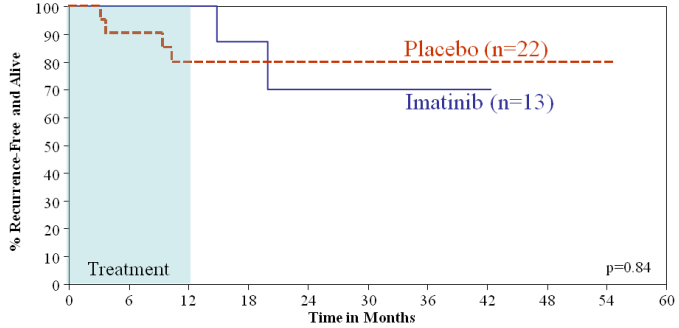


Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

RFS for Wildtype

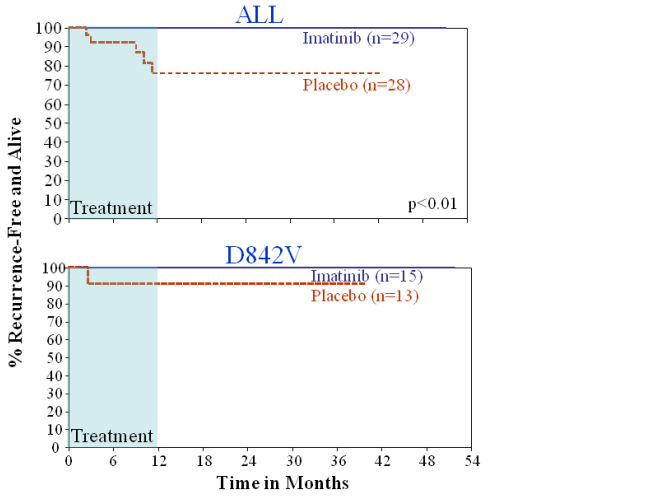


RFS for Exon 9



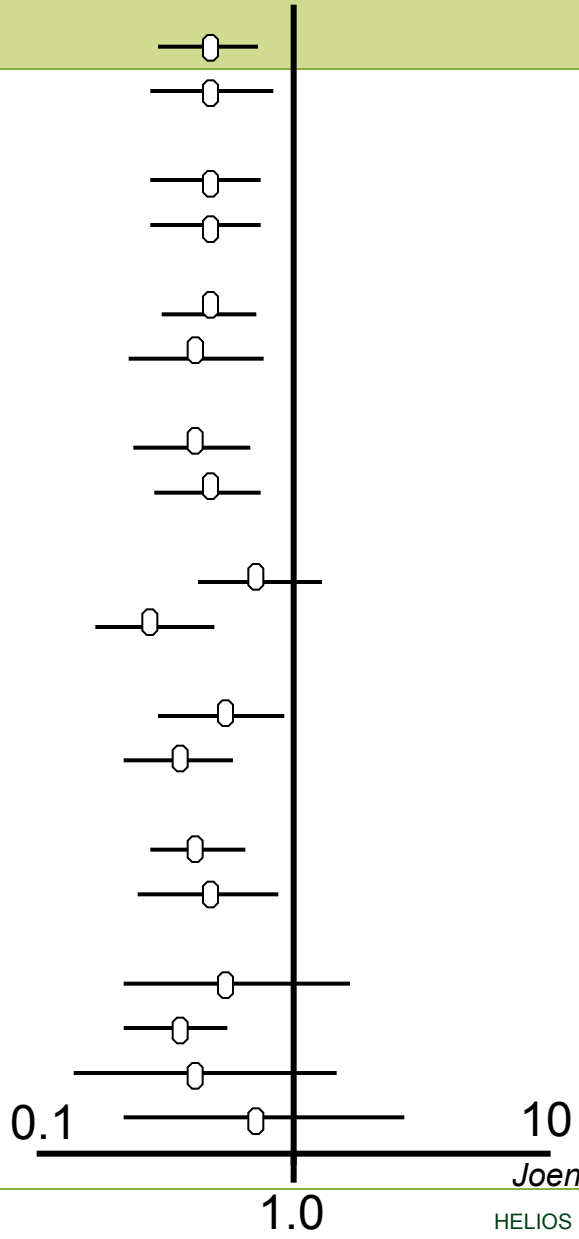
Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

RFS for PDGFRA



Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

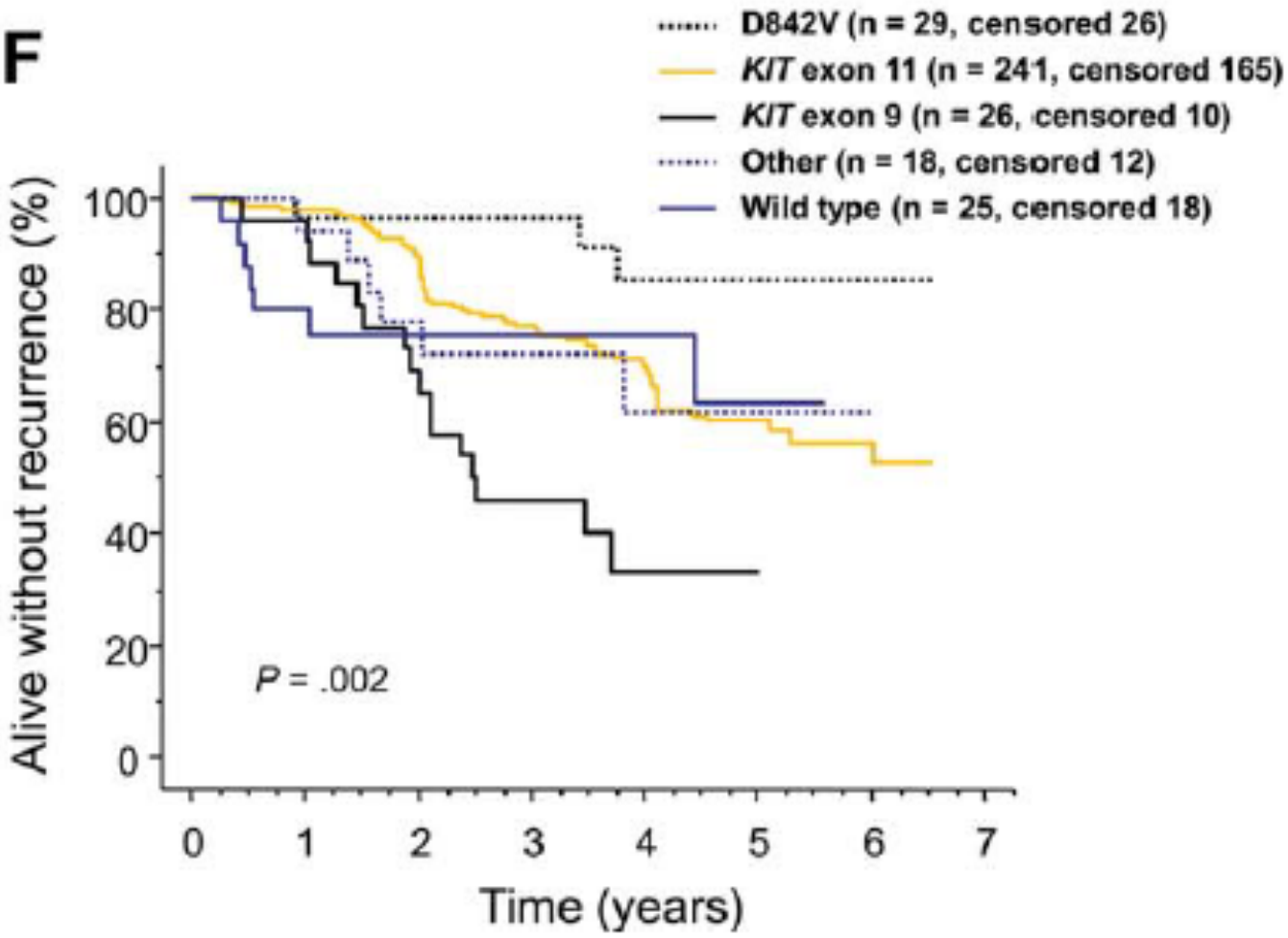
Subgroup	No. of patients	Hazard ratio (95% CI), RFS	*P* value
		36 mo better — *12 mo better*	
Age			
≤65	256	0.47 (0.30-0.74)	.001
>65	141	0.49 (0.28-0.85)	.01
Sex			
Male	201	0.46 (0.28-0.76)	.002
Female	196	0.46 (0.28-0.76)	.002
Tumor site			
Stomach	202	0.42 (0.23-0.78)	.006
Other	195	0.47 (0.31-0.73)	<.001
Tumor size			
≤ 10 cm	219	0.40 (0.24-0.69)	<.001
>10 cm	176	0.47 (0.29-0.76)	.002
Mitoses/50 HPF (local)			
≤ 10 mitoses	209	0.76 (0.43-1.32)	.33
> 10 mitoses	154	0.29 (0.17-0.50)	<.001
Mitoses/50 HPF (central)			
≤ 10 mitoses	238	0.53 (0.30-0.94)	.03
> 10 mitoses	133	0.36 (0.22-0.59)	<.001
Tumor rupture			
No	318	0.43 (0.28-0.66)	<.001
Yes	79	0.47 (0.25-0.89)	.02
Tumor mutation site			
KIT exon 9	26	0.62 (0.22-1.70)	.35
KIT exon 11	256	0.35 (0.22-0.56)	<.001
Wild type	33	0.41 (0.14-1.51)	.18
Other	51	0.78 (0.22-2.78)	.71



Joensuu, ..., Reichardt, JAMA 307:1265-1272, 2012

Risk Factors for Gastrointestinal Stromal Tumor Recurrence in Patients Treated With Adjuvant Imatinib

Heikki Joensuu, MD[1]; Mikael Eriksson, MD[2]; Kirsten Sundby Hall, MD[3]; Jörg T. Hartmann, MD[4]; Daniel Pink, MD[5]; Jochen Schütte, MD[6]; Giuliano Ramadori, MD[7]; Peter Hohenberger, MD[8]; Justus Duyster, MD[9]; Salah-Eddin Al-Batran, MD[10]; Marcus Schlemmer, MD[11]; Sebastian Bauer, MD[12]; Eva Wardelmann, MD[13]; Maarit Sarlomo-Rikala, MD[14]; Bengt Nilsson, MD[15]; Harri Sihto, PhD[16]; Karla V. Ballman, PhD[17]; Mika Leinonen, MSci[18]; Ronald P. DeMatteo, MD[19]; and Peter Reichardt, MD[5]

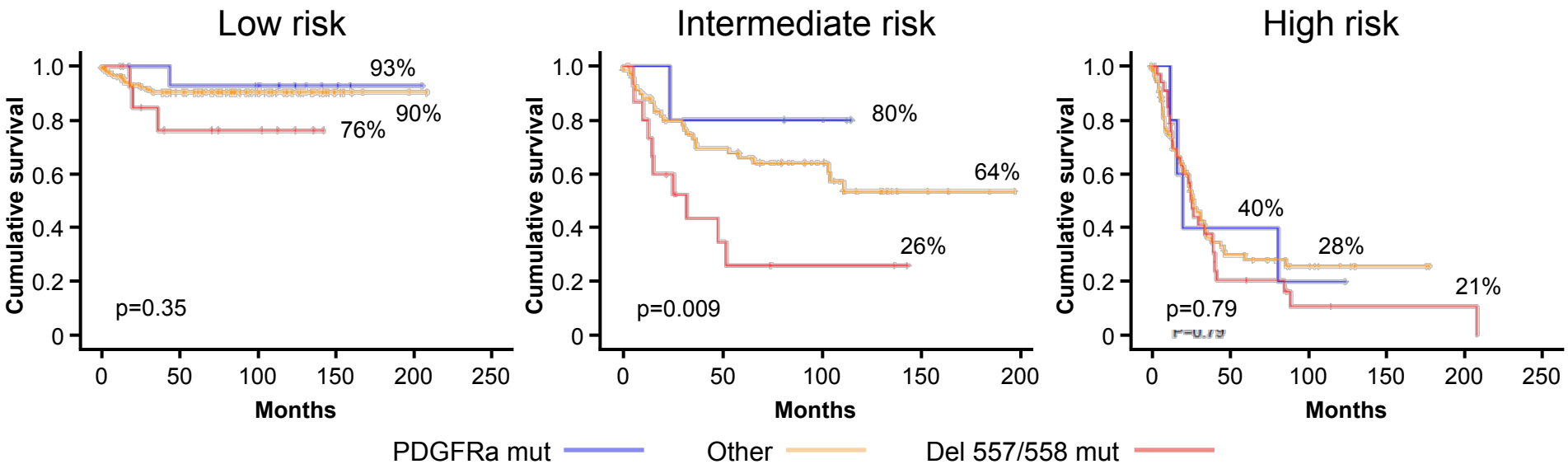


Cancer August 1, 2014

Integrating genotype in risk classification for GIST recurrence: a Spanish group for sarcoma research (GEIS) study

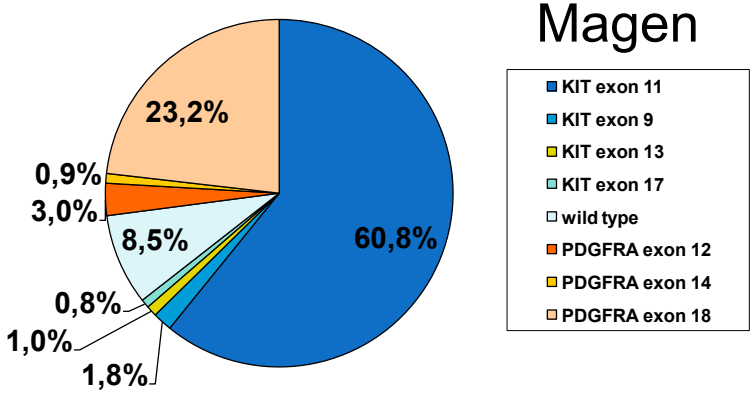
- Analysis of the influence of genotype factors for Miettinen risk categories in 394 patients with localised GIST

7-year actuarial RFS according to Miettinen risk category and prognostic genotype



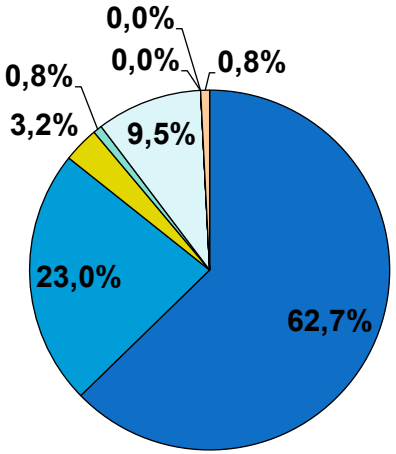
Martin-Broto J et al. ESMO 2014

Korrelation von *KIT*- und *PDGFRA*-Mutationen und Primärlokalisation



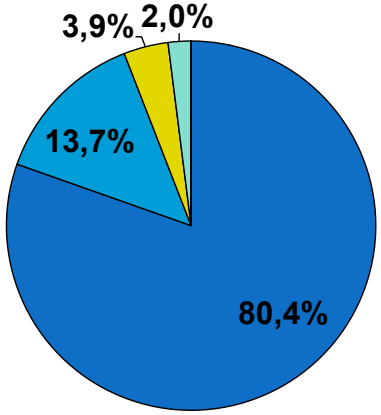
Magen

- KIT exon 11
- KIT exon 9
- KIT exon 13
- KIT exon 17
- wild type
- PDGFRA exon 12
- PDGFRA exon 14
- PDGFRA exon 18



Dünndarm

- KIT exon 11
- KIT exon 9
- KIT exon 13
- KIT exon 17
- wild type
- PDGFRA exon 12
- PDGFRA exon 14
- PDGFRA exon 18



Rektum

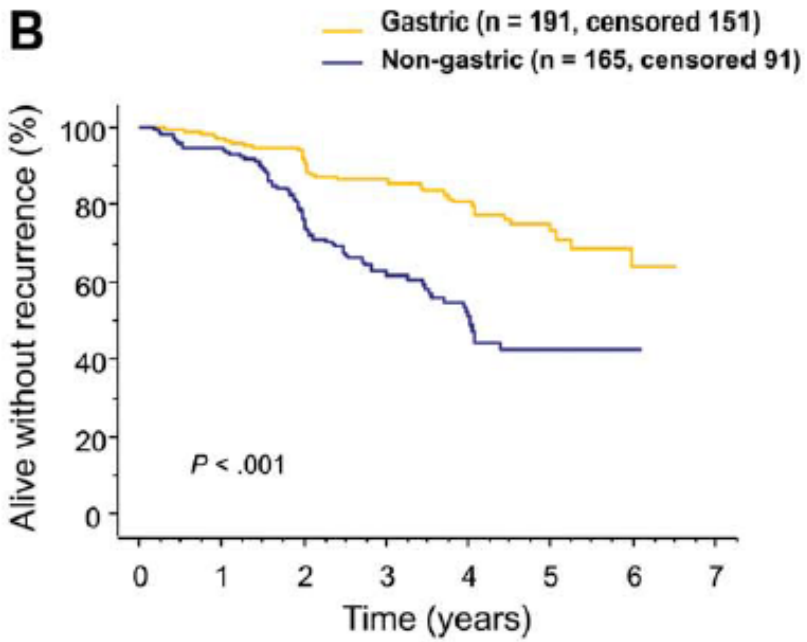
- KIT exon 11
- KIT exon 9
- KIT exon 13
- KIT exon 17
- wild type
- PDGFRA exon 12
- PDGFRA exon 14
- PDGFRA exon 18

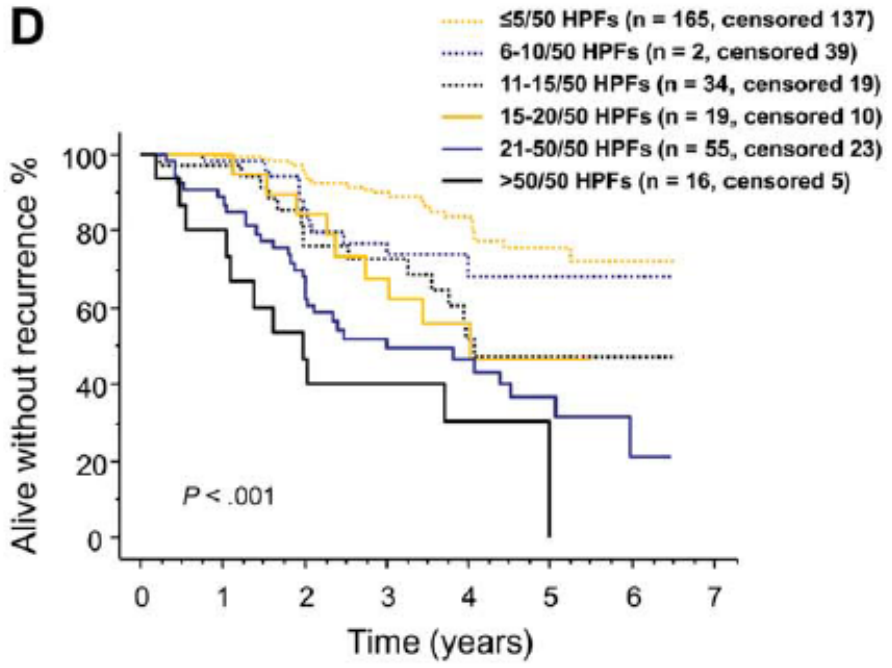
GSRCB* (n=1231)

*GSRCB = GIST and Sarcoma Registry Cologne/Bonn

Risk Factors for Gastrointestinal Stromal Tumor Recurrence in Patients Treated With Adjuvant Imatinib

Heikki Joensuu, MD[1]; Mikael Eriksson, MD[2]; Kirsten Sundby Hall, MD[3]; Jörg T. Hartmann, MD[4]; Daniel Pink, MD[5]; Jochen Schütte, MD[6]; Giuliano Ramadori, MD[7]; Peter Hohenberger, MD[8]; Justus Duyster, MD[9]; Salah-Eddin Al-Batran, MD[10]; Marcus Schlemmer, MD[11]; Sebastian Bauer, MD[12]; Eva Wardelmann, MD[13]; Maarit Sarlomo-Rikala, MD[14]; Bengt Nilsson, MD[15]; Harri Sihto, PhD[16]; Karla V. Ballman, PhD[17]; Mika Leinonen, MSci[18]; Ronald P. DeMatteo, MD[19]; and Peter Reichardt, MD[5]





Cancer August 1, 2014

Risk Factors for Gastrointestinal Stromal Tumor Recurrence in Patients Treated With Adjuvant Imatinib

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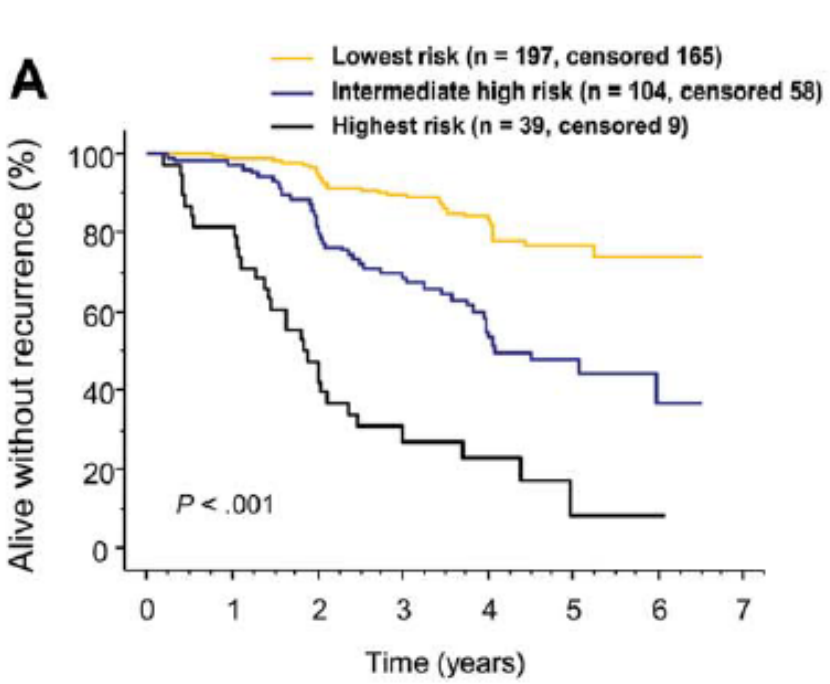
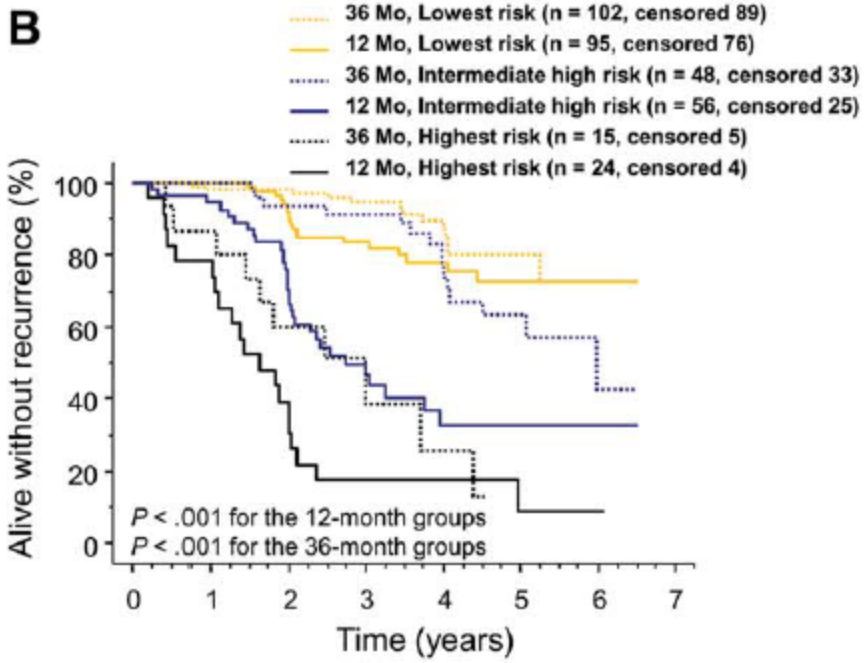
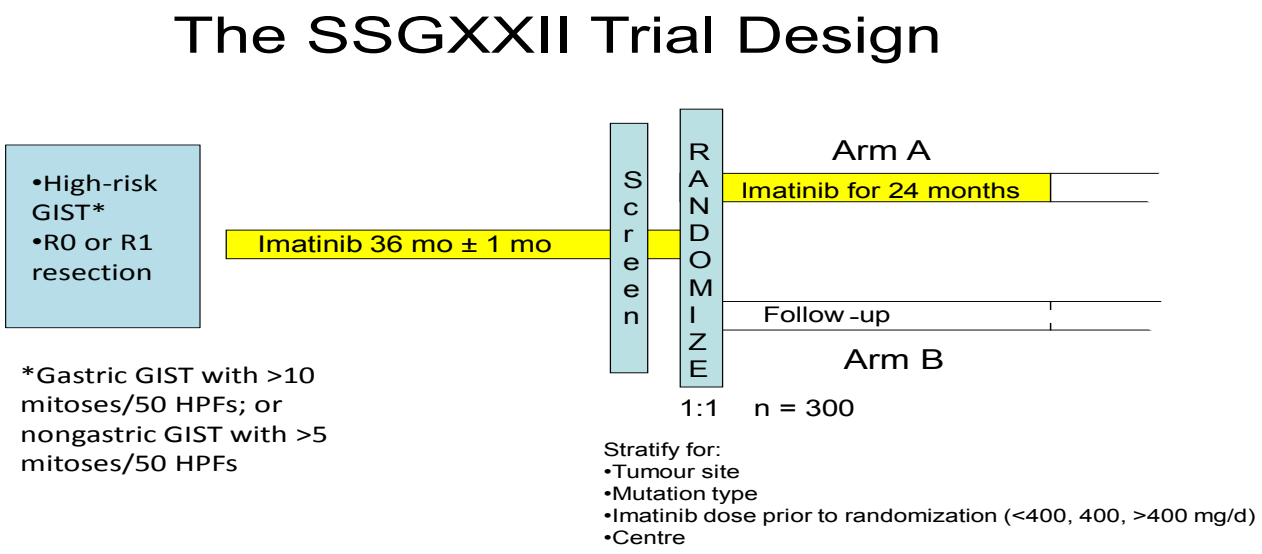




highest risk, gastric GIST with > 50 mitoses or non-gastric GIST with > 20 mitoses per 50 high-power fields).

Cancer August 1, 2014

Three versus five years of adjuvant imatinib as treatment of patients with operable GIST with a high risk for recurrence: A randomised phase III study



5. High risk of tumour recurrence following surgery and 3 years of adjuvant imatinib defined as one of the following:

1) gastric GIST with a mitotic count >10/50 HPFs (HPF, high power field of the microscope),
2) non-gastric GIST with a mitotic count >5/50 HPFs, or
3) tumour rupture

Tumour rupture may have occurred before or at surgery. Tumour rupture is defined by spillage of the tumour contents into the abdominal cavity. A core needle biopsy from the tumour, or tumour bleed with no apparent spillage of the tumour contents, are not considered ruptures.

clinical practice guidelines

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Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

plete resection [15]. Therefore, adjuvant therapy with imatinib for 3 years is the standard treatment of patients with a significant risk of relapse [I, A]. Adjuvant therapy should not be considered when the risk is low. There is room for shared decision-making when the risk is intermediate [16].

Mutational analysis is critical to making a clinical decision about adjuvant therapy. In fact, there is consensus that PDGFRA D842V-mutated GISTs should not be treated with any adjuvant therapy, given the lack of sensitivity of this genotype both *in vitro* and *in vivo* [IV, A]. Given the data supporting the use of a

higher dose of imatinib (800 mg daily) in the case of an exon 9 *KIT* mutation in advanced GIST, many clinicians prefer to use this dose even in the adjuvant setting for this genotype [17–19].

by any controlled trial in the adjuvant setting. There is consensus on avoiding adjuvant treatment in neurofibromatosis 1-related GISTs, which are insensitive to imatinib in the advanced setting. On the other hand, a consensus is lacking among experts about whether wild-type SDH-negative GISTs should be treated with adjuvant therapy. This reflects their lower sensitivity to imatinib, as well as their peculiar natural history, which is often more in-