

Helios Klinikum Berlin-Buch
Department of Oncology and Palliative Care
Sarcoma Center
Chairman of the German Sarcoma Foundation



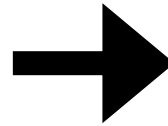
GIST: Localized, operable primary tumor

Peter Reichardt

GIST: local therapy

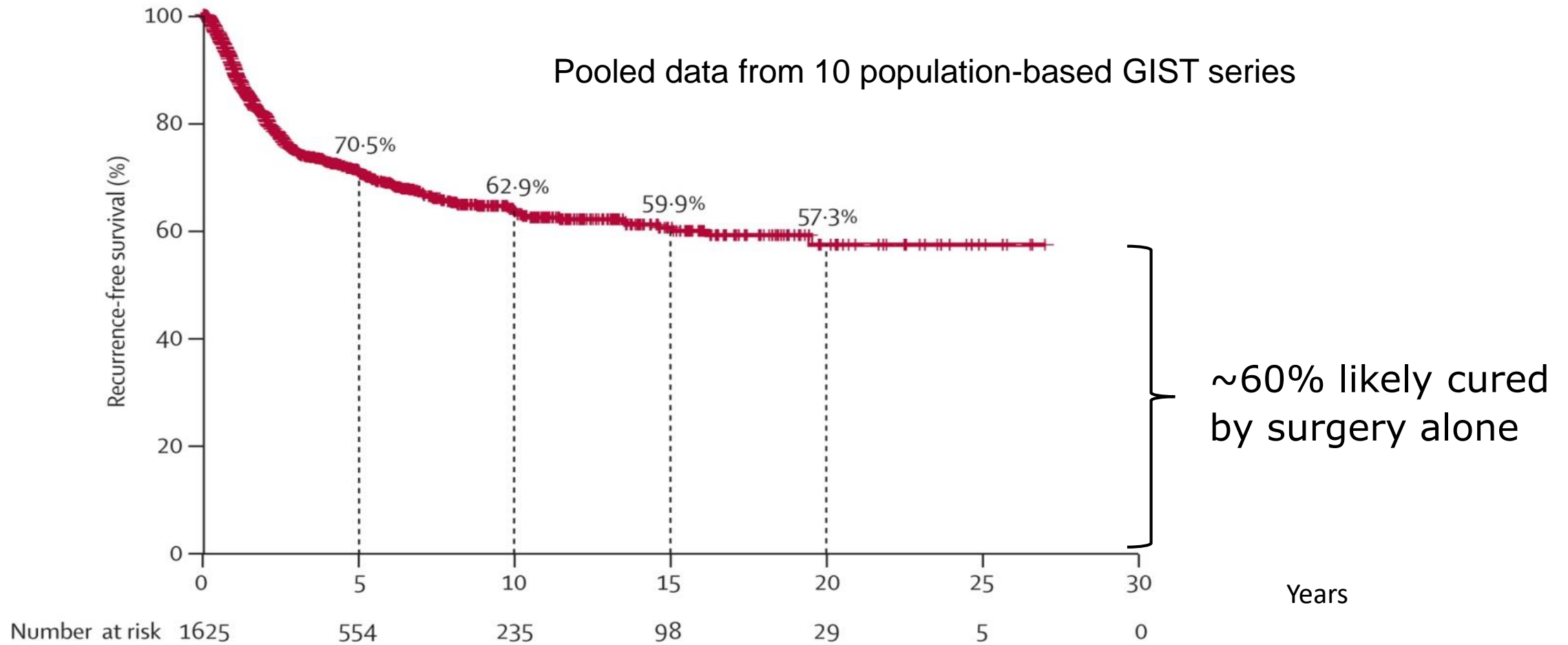
- tumors >2 cm: biopsy / excision (Rectum: any size)
- localized GIST: complete surgical removal
- preoperative systemic therapy to avoid mutilating surgery (mutational analysis mandatory)

Aims of neoadjuvant therapy



- Downsizing of borderline resectable GIST
- Avoid mutilating surgery

Risk of recurrence after surgery alone



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

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	} 34*	} 57*
3b	>10.0 cm, ≤5/50 HPF	12	52		
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	} 86*	} 71*
6b	>10.0 cm >5/50 HPF	86	90		

*very low numbers

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

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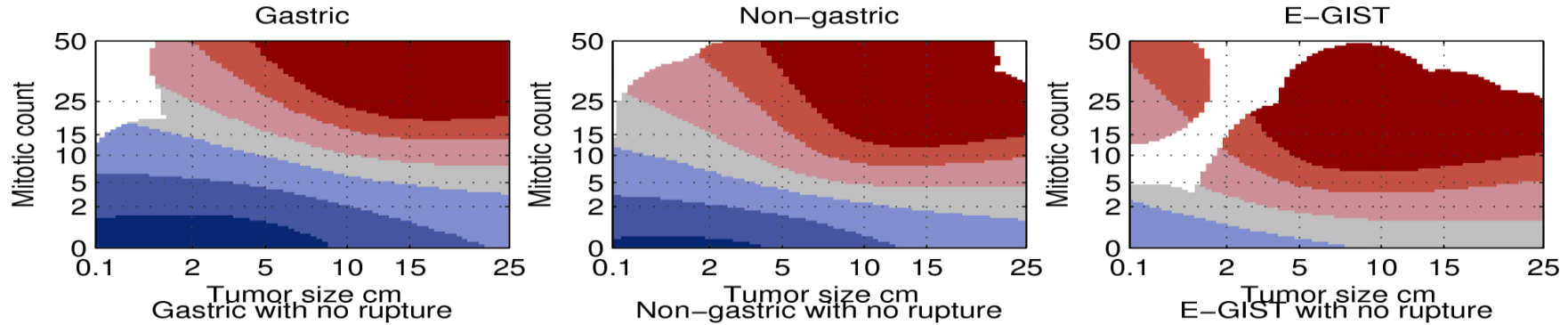
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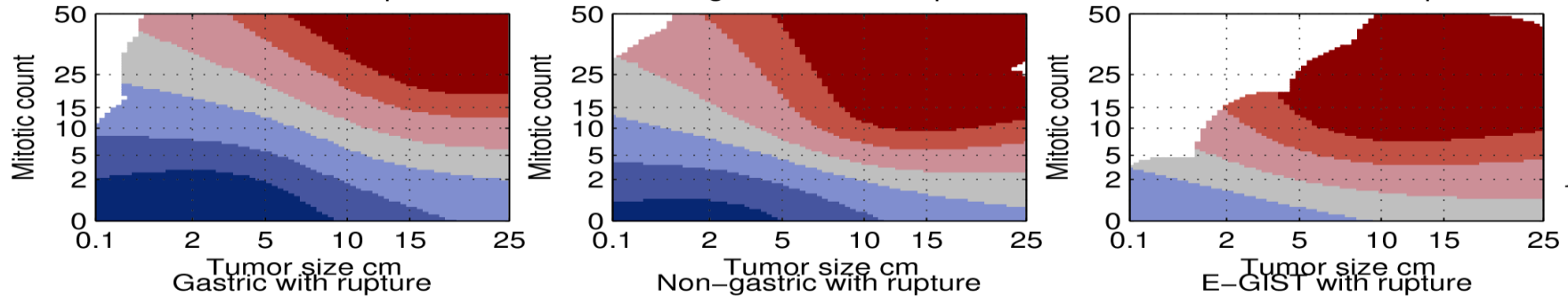
Miettinen M, Lasota J., *Sem Diagn Pathol* 2006;23:70-83

Prognostic contour maps, 10-year RFS

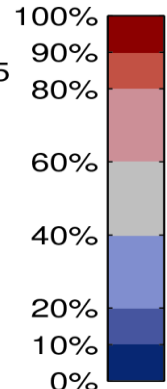
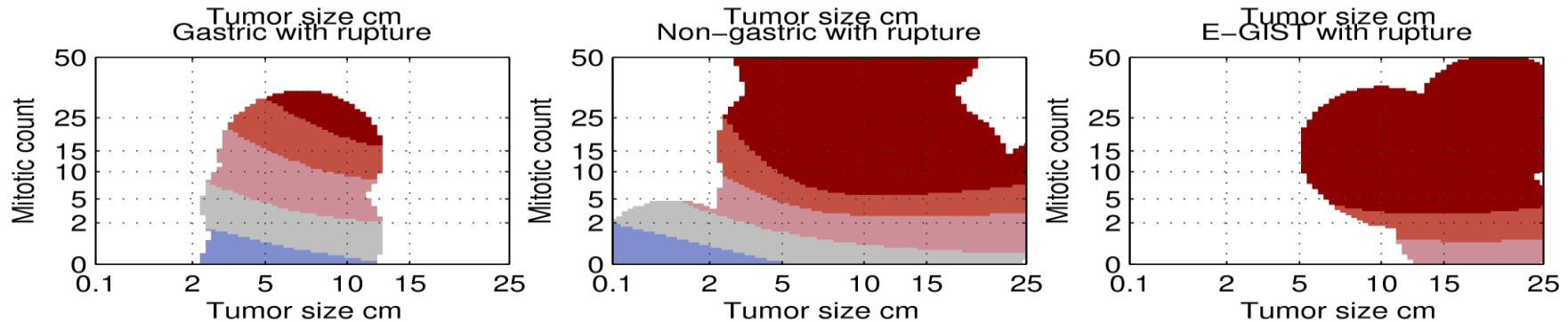
Rupture ?



No rupture

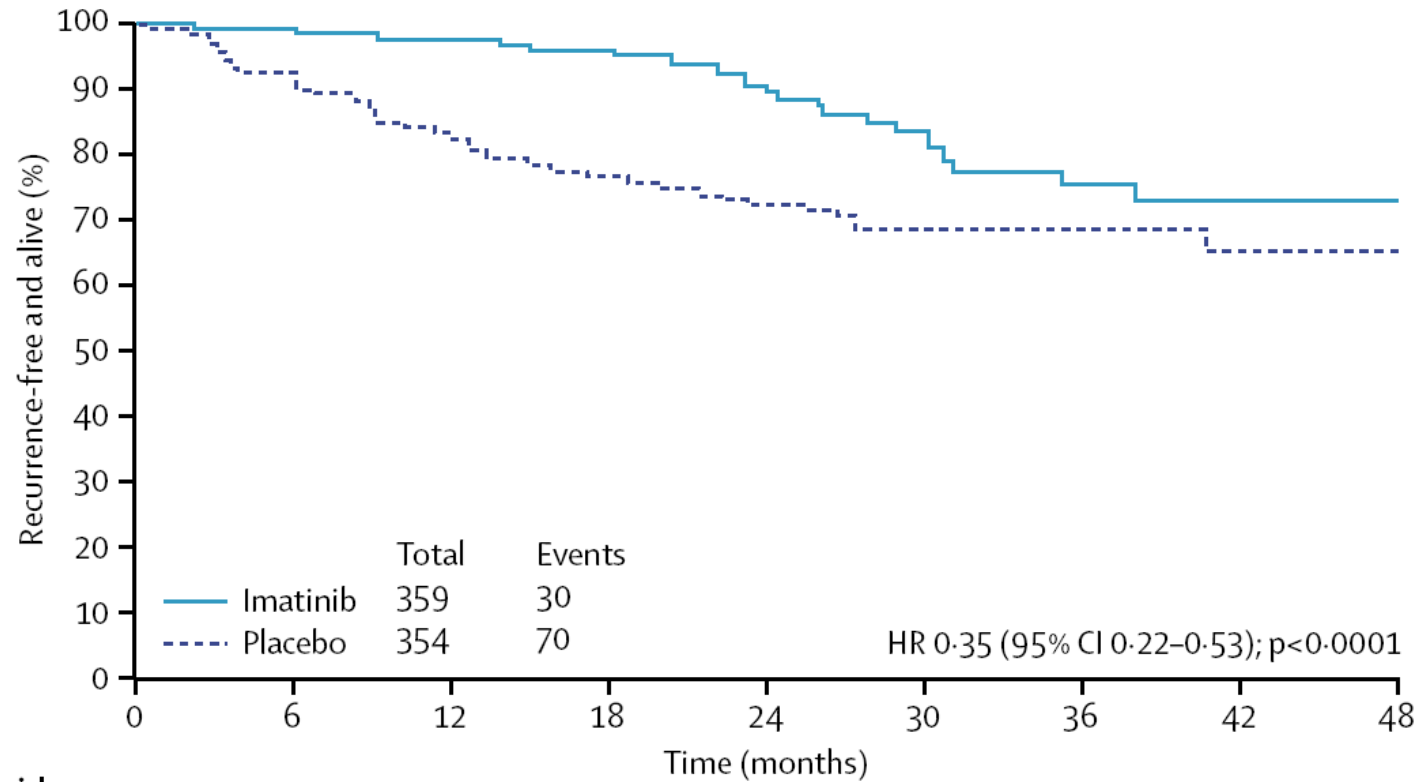


Rupture present



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

Z9001: Recurrence-Free Survival

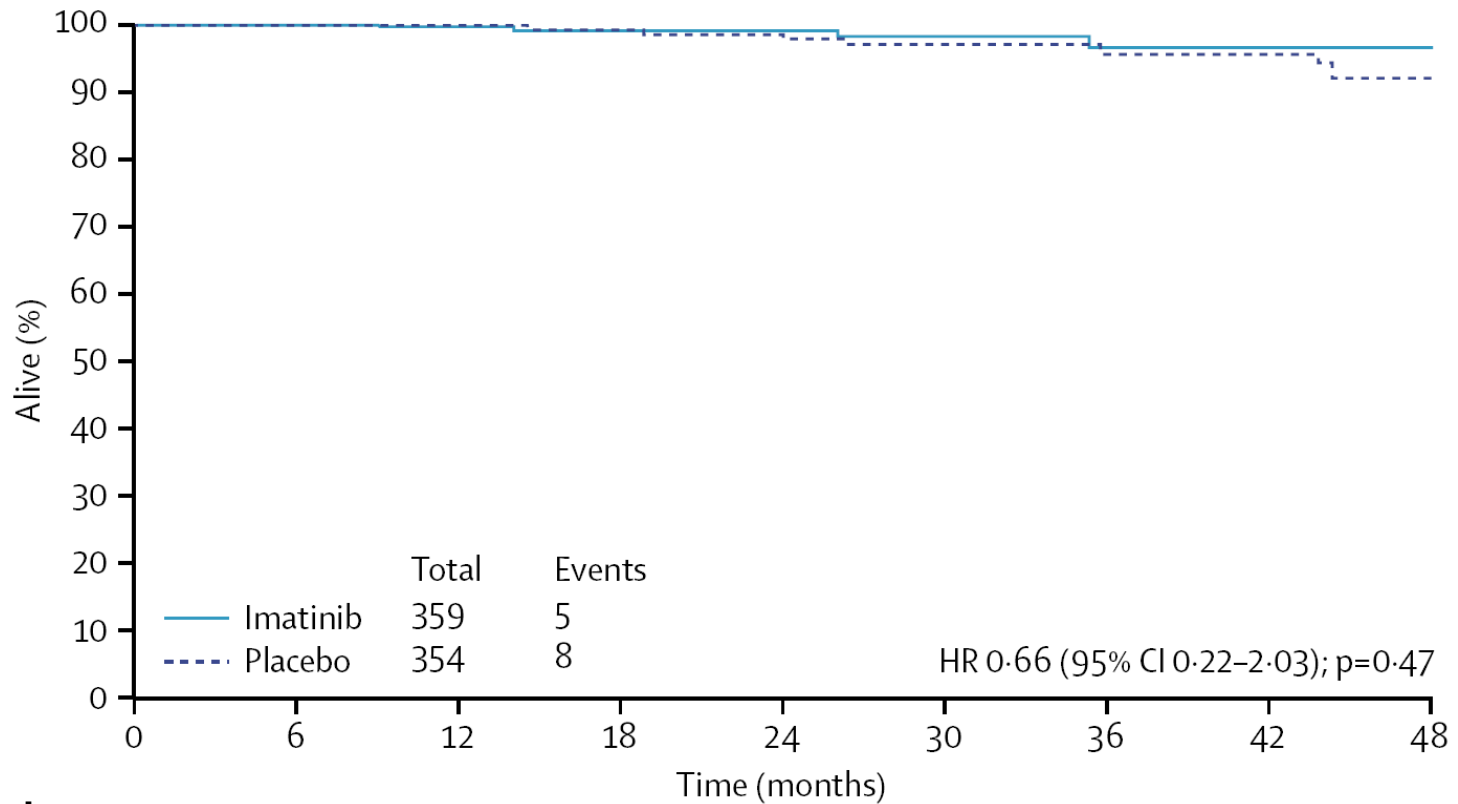


Number at risk

	0	6	12	18	24	30	36	42	48
Placebo	354	188	89	34	8				
Imatinib	359	207	105	33	6				

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

Z9001: Overall Survival



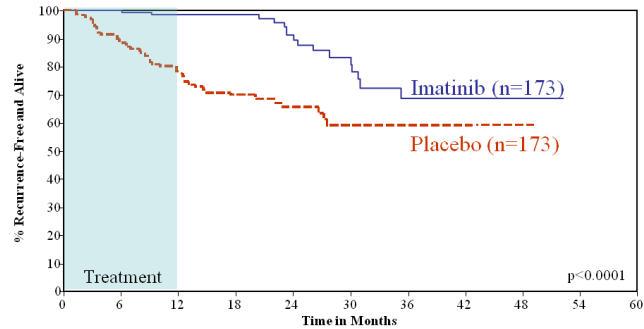
Number at Risk

	0	6	12	18	24	30	36	42	48
Imatinib	359	241	151	58	15				
Placebo	354	226	137	51	15				

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

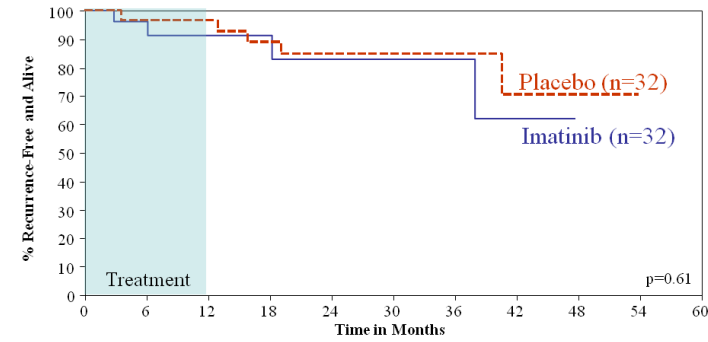
Influence of mutational status on outcome of adjuvant imatinib

RFS for Exon 11

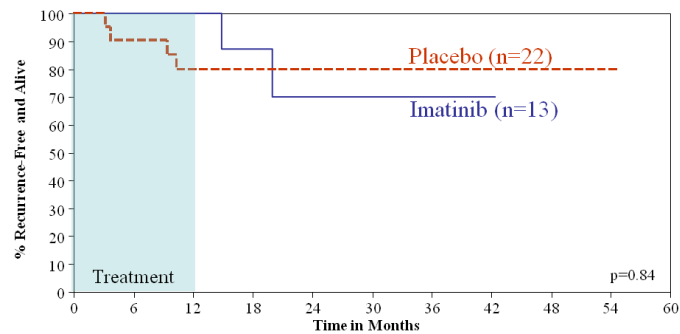


Corless CL et al. JCO 2010; 28(15s): suppl; abstract 10006.

RFS for Wildtype

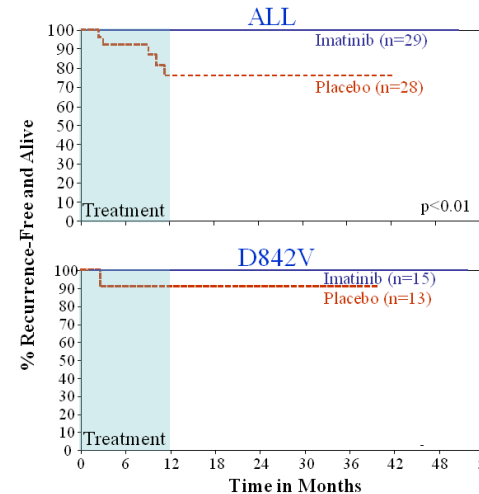


RFS for Exon 9



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

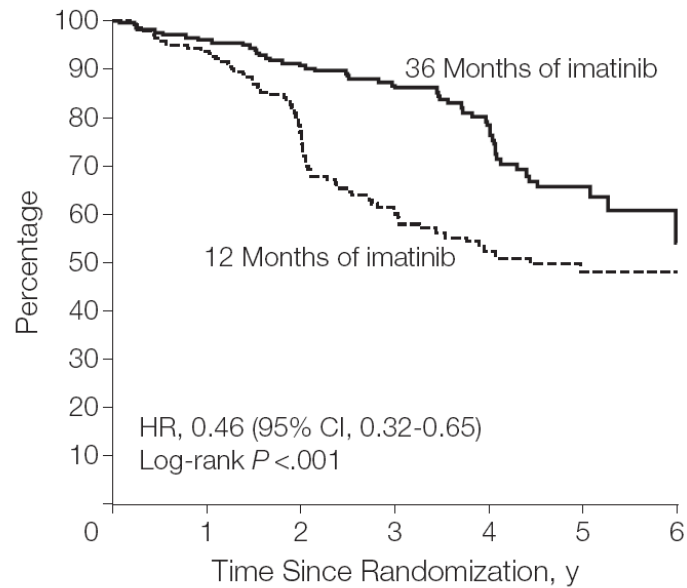
RFS for PDGFRA



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

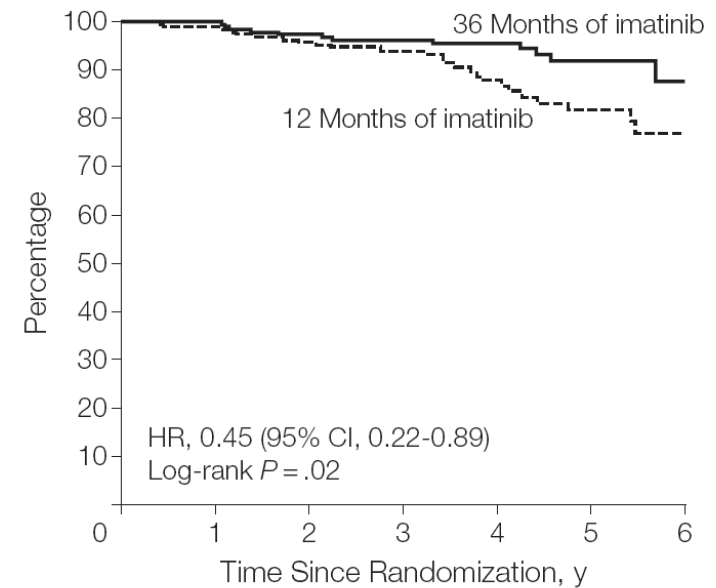
SSGXVIII/AIO: RFS and OS

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



No. of patients	198	184	173	133	82	39	8
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

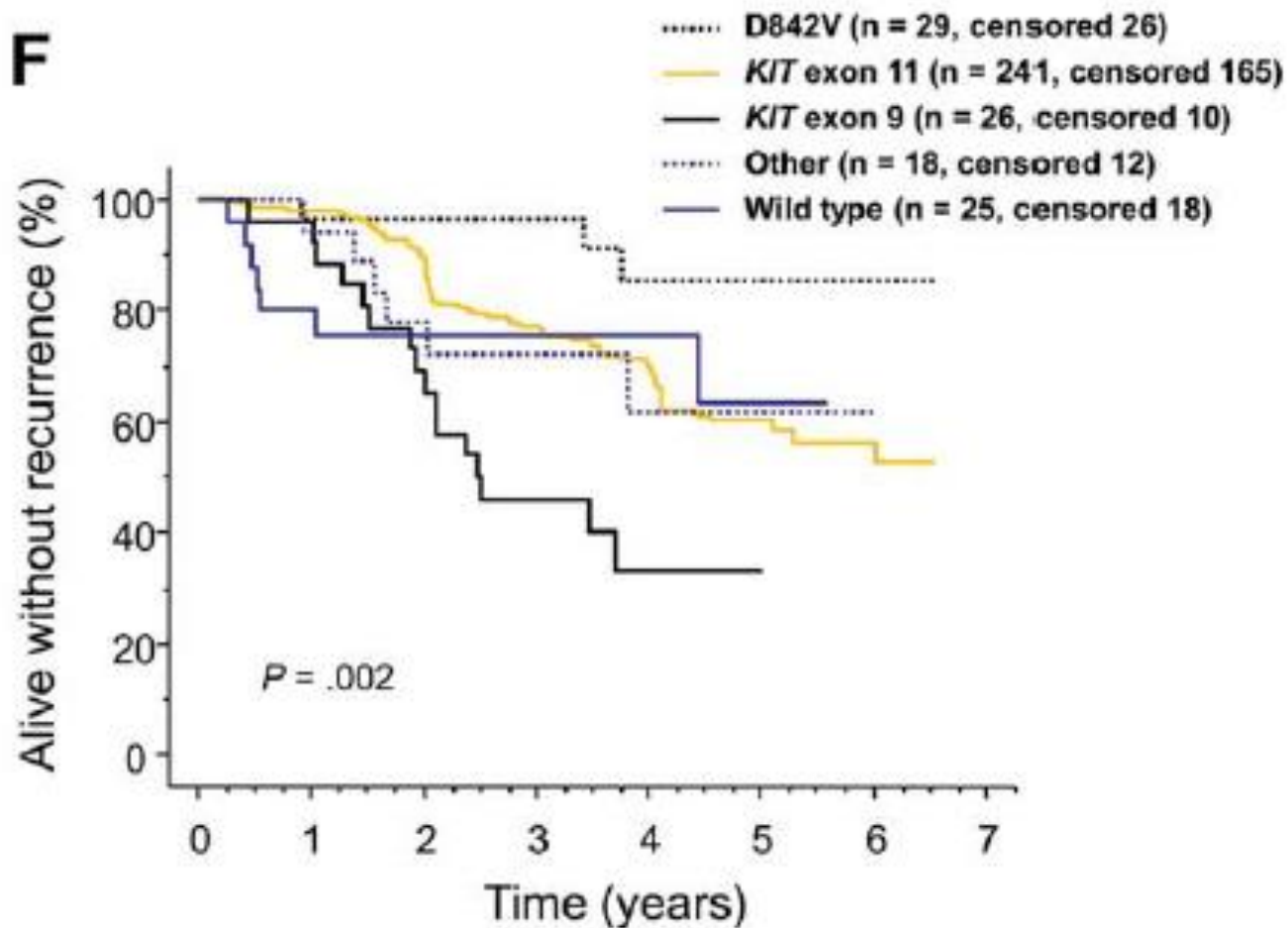


No. of patients	198	192	184	152	100	56	13
36 Months of imatinib	198	192	184	152	100	56	13
12 Months of imatinib	199	188	176	140	87	46	20

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

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

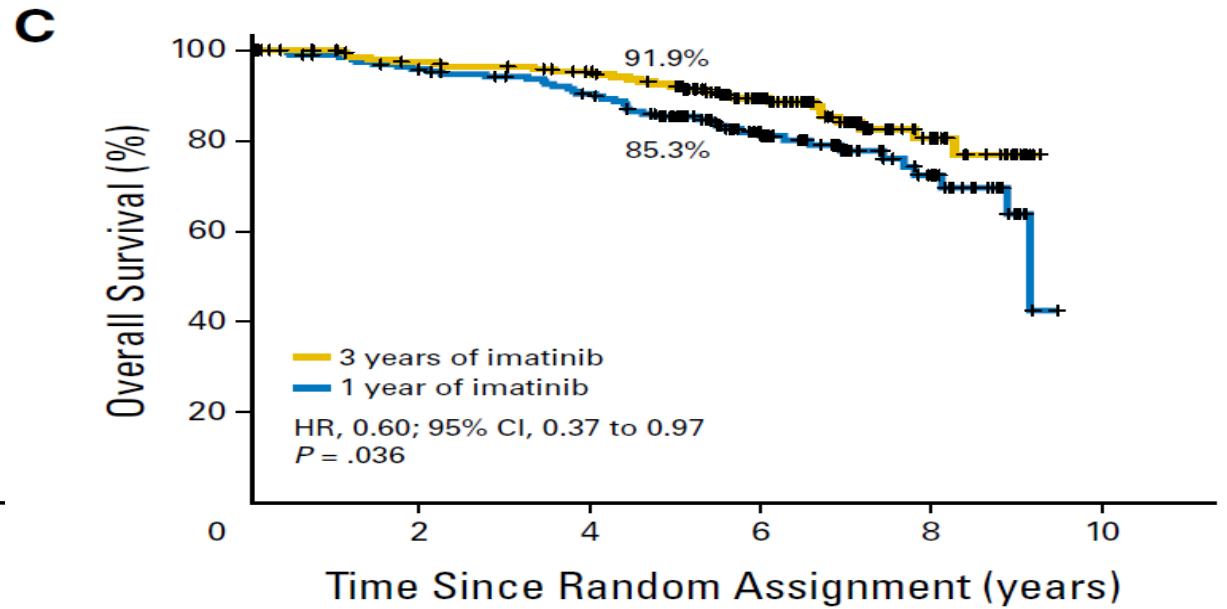
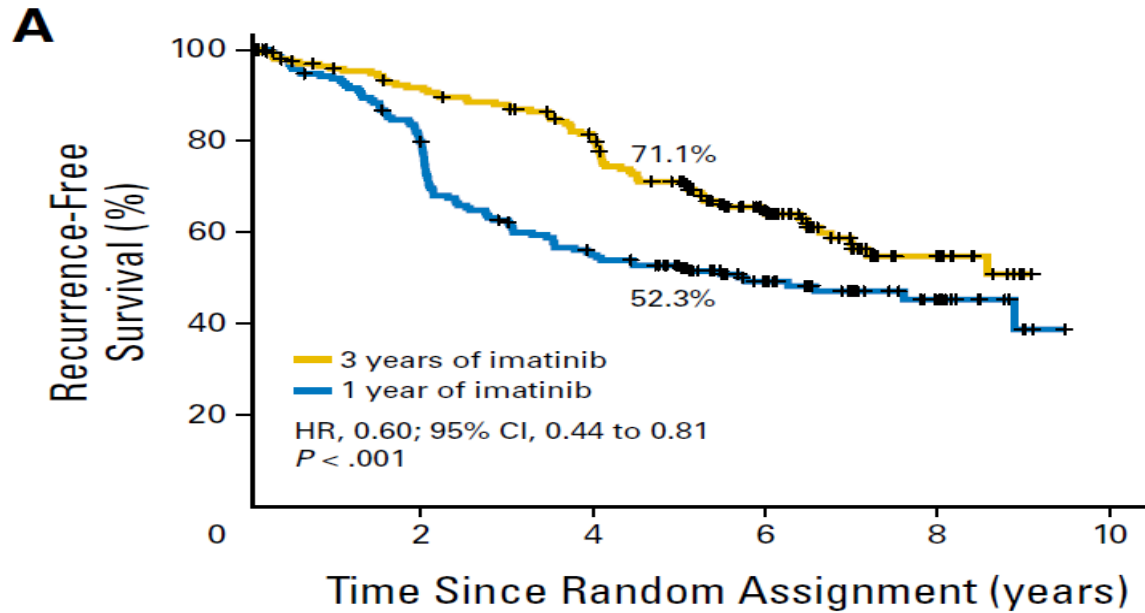
Heikki Joensuu, MD¹; Mikael Eriksson, MD²; Kirsten Sundby Hall, MD³; Jörg T. Hartmann, MD⁴; Daniel Pink, MD⁵;
Jochen Schütte, MD⁶; Giuliano Ramadori, MD⁷; Peter Hohenberger, MD⁸; Justus Duyster, MD⁹;
Salah-Eddin Al-Batran, MD¹⁰; Marcus Schlemmer, MD¹¹; Sebastian Bauer, MD¹²; Eva Wardelmann, MD¹³;
Maarit Sarlomo-Rikala, MD¹⁴; Bengt Nilsson, MD¹⁵; Harri Sihto, PhD¹⁶; Karla V. Ballman, PhD¹⁷; Mika Leinonen, MSc¹⁸;
Ronald P. DeMatteo, MD¹⁹; and Peter Reichardt, MD⁵



Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial

Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, Annette Reichardt, Jörg T. Hartmann, Daniel Pink, Giuliano Ramadori, Peter Hohenberger, Salah-Eddin Al-Batran, Marcus Schlemmer, Sebastian Bauer, Eva Wardelmann, Bengt Nilsson, Harri Sihto, Petri Bono, Raija Kallio, Jouni Junnila, Thor Alvegård, and Peter Reichardt

Recurrence-free Survival



Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas

Paolo G. Casali, Axel Le Cesne, Andres Poveda Velasco, Dusan Kotasek, Piotr Rutkowski, Peter Hohenberger, Elena Fumagalli, Ian R. Judson, Antoine Italiano, Hans Gelderblom, Antoine Adenis, Jörg T. Hartmann, Florence Duffaud, David Goldstein, Javier M. Broto, Alessandro Gronchi, Angelo P. Dei Tos, Sandrine MARRÉAUD, Winette T.A. van der Graaf, John R. Zalberg, Saskia Litière, and Jean-Yves Blay

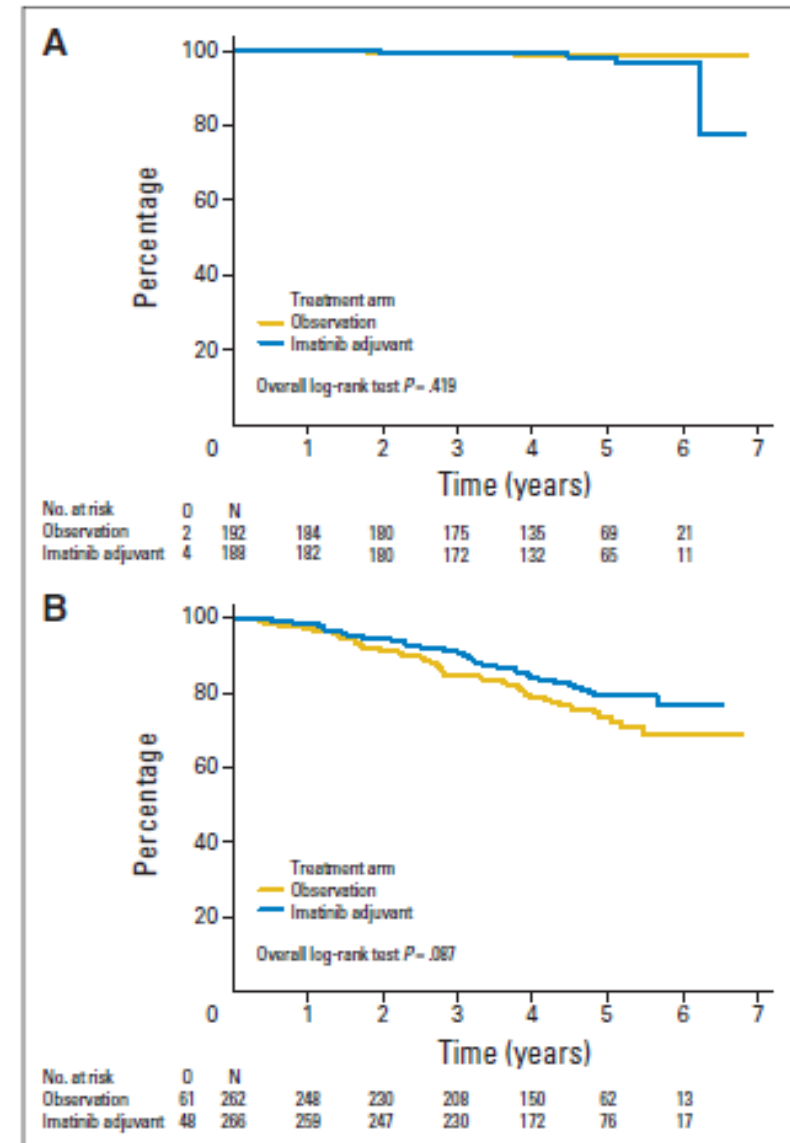
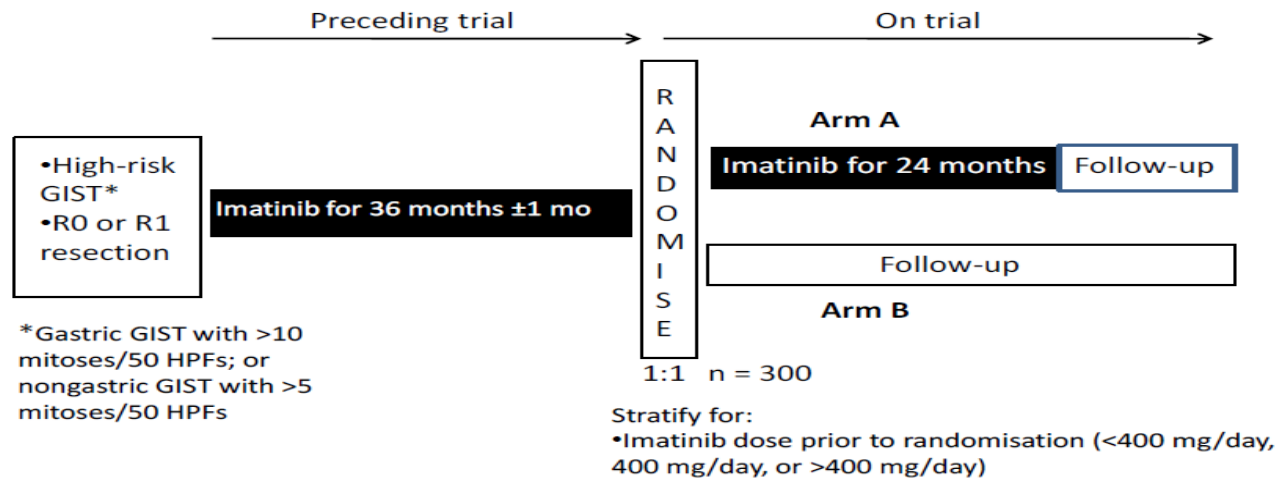


Fig 3. Imatinib monotherapy failure-free survival in (A) intermediate- and (B) high-risk patients, classified according to 2002 National Institutes of Health classification. N, number of patients; O, number of observed events.

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

Trial design



NUMBER OF PATIENTS	300 patients to be randomised in 1:1 ratio, 150 to imatinib for further 24 months and 150 to stop imatinib.
RANDOMISATION	Central randomisation. At randomisation, the patients are stratified by the imatinib dose preceding randomisation (< 400 mg/day, 400 mg/day, or >400 mg/day). The centres will keep a log of patients who received the informed consent.



Abstract #11503

AIO

Three versus one year of adjuvant imatinib for high-risk gastrointestinal stromal tumor (GIST): Survival analysis of a randomized trial after 10 years of follow-up

Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, Annette Reichardt, Barbara Hermes, Jochen Schütte, Silke Cameron, Peter Hohenberger, Philipp J Jost, Salah-Eddin Al-Batran, Lars H Lindner, Sebastian Bauer, Eva Wardelmann, Bengt Nilsson, Raija Kallio, Panu Jaakkola, Jouni Junnila, Thor Alvegård, Peter Reichardt

Justification for the 3rd analysis of the SSGXVIII/AIO trial

- It is unknown whether imatinib improves OS after extended follow-up
- Little is known about the long-term safety of adjuvant imatinib

The study protocol was amended in April 2017 to allow the 3rd analysis of the trial

- The analysis to be carried out when the last patient entered to the trial was followed-up for 10 years¹

¹The maximum follow-up period in the study protocol

Key inclusion criteria

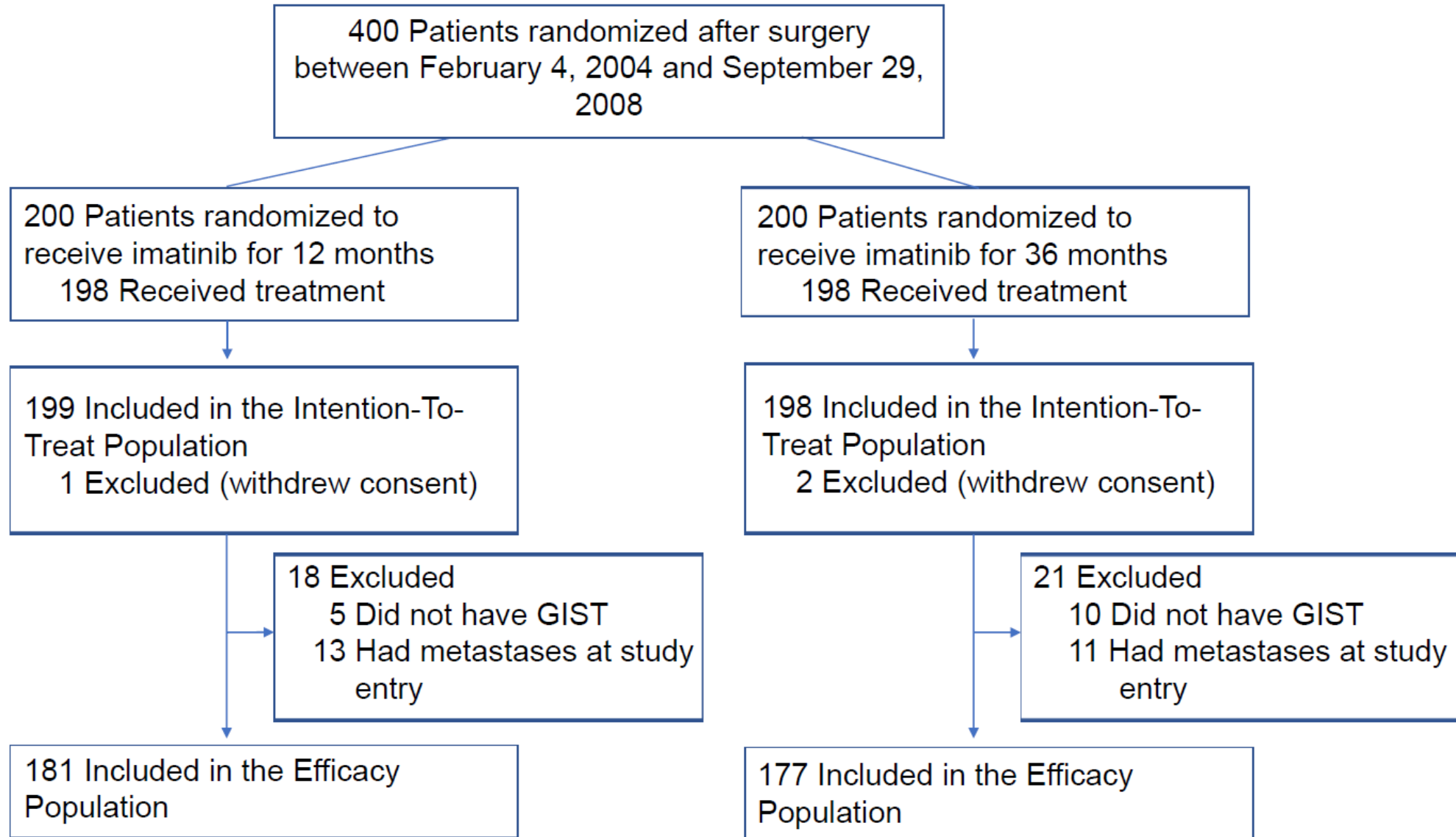
- Histologically confirmed KIT-positive GIST
- High risk of recurrence according to the modified Consensus Criteria^{1,2}:
 - Tumor size >10 cm *or*
 - Tumor mitosis count >10/50 HPFs *or*
 - Size >5 cm and mitosis count >5/50 HPFs *or*
 - Tumor rupture spontaneously or at surgery

HPF = high-power field of the microscope

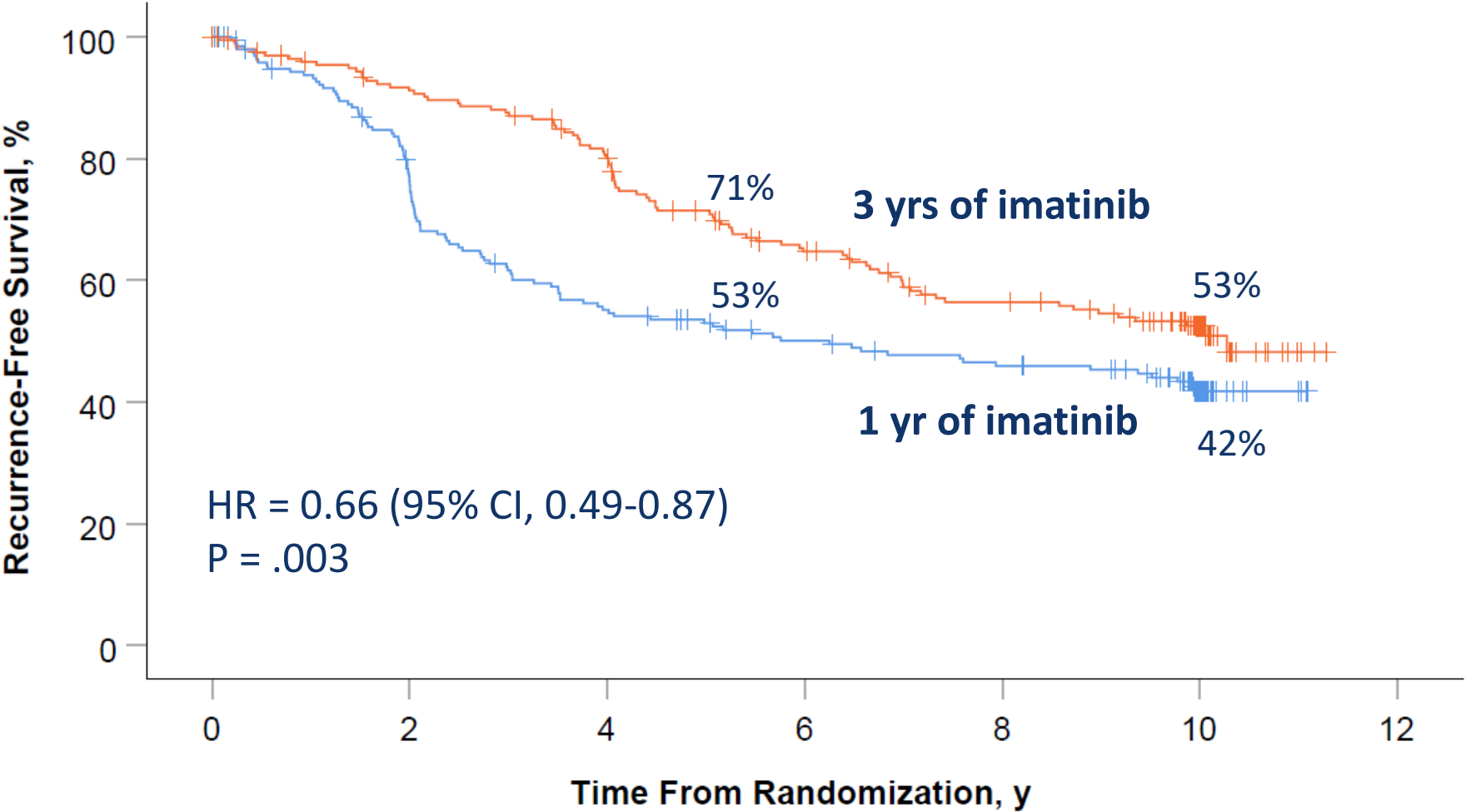
¹Fletcher CD et al. Hum Pathol 2002; 33:459-65

²Joensuu H. Hum Pathol 2008;39:1411-9

CONSORT Diagram

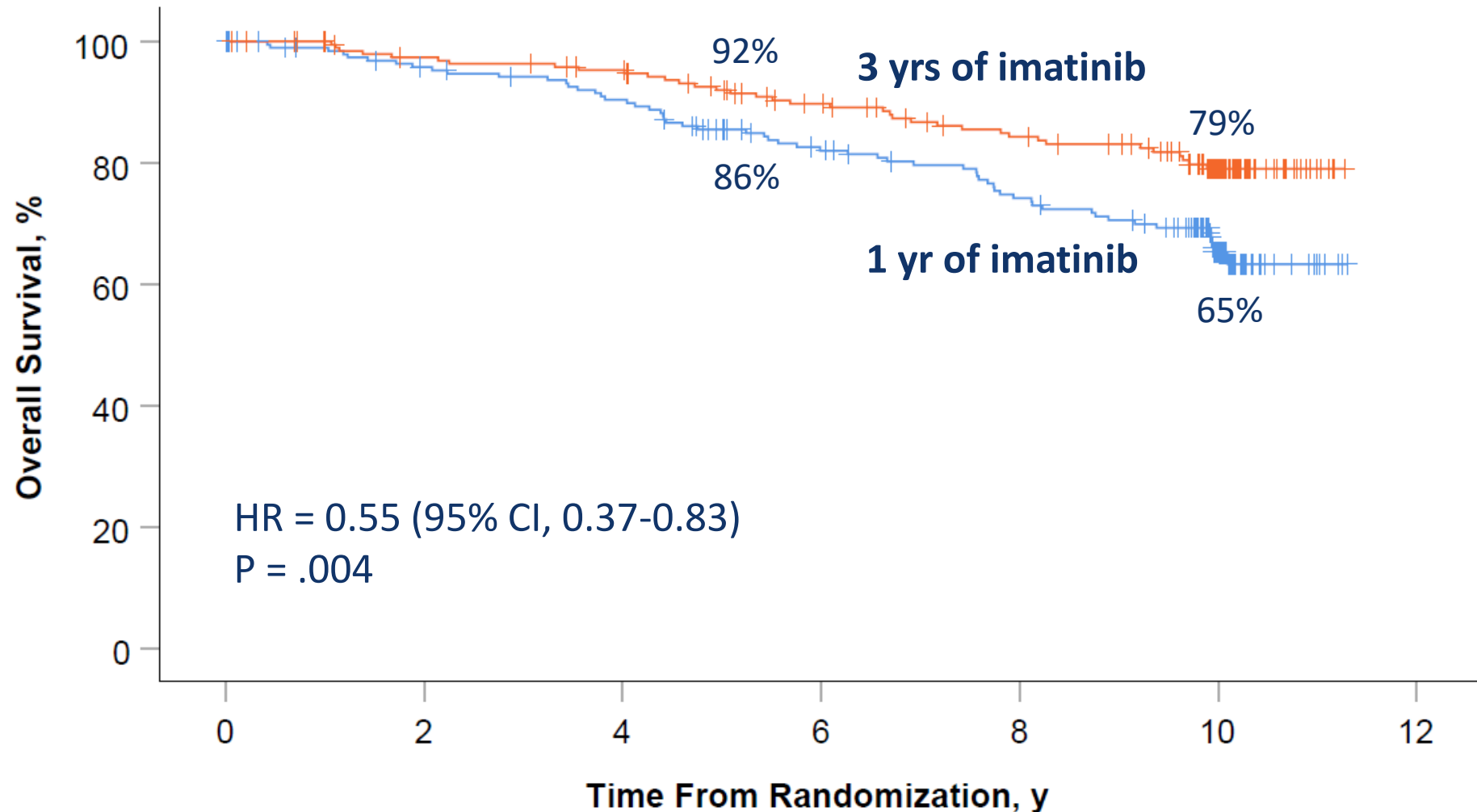


Recurrence-free survival in the Intention-To-Treat Population



No. at risk	0	2	4	6	8	10	12
36 months	198	174	150	114	93	47	0
12 months	199	141	102	86	77	38	0

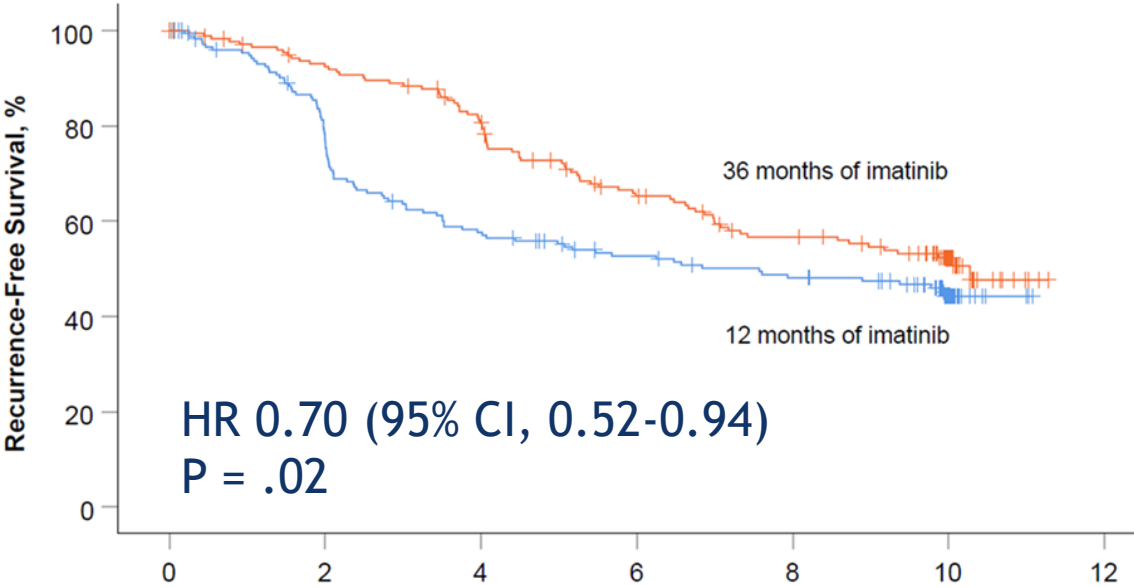
Overall survival in the Intention-To-Treat Population



No. at risk	0	2	4	6	8	10	12
36 months	198	185	178	155	138	76	0
12 months	199	179	167	140	123	60	0

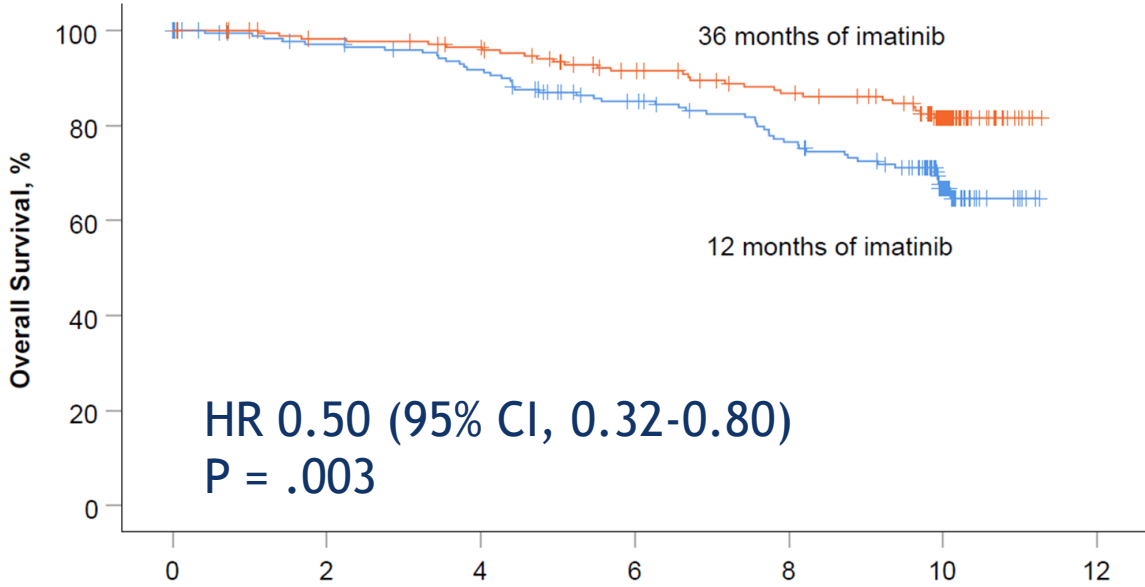
RFS and overall survival in the Efficacy Population¹

RFS



No. at risk	0	2	4	6	8	10	12
36 months	177	158	135	103	84	43	0
12 months	181	130	97	82	73	37	0

OS



No. at risk	0	2	4	6	8	10	12
36 months	177	167	161	141	127	71	0
12 months	181	165	154	133	116	58	0

¹Patients who signed informed consent, had GIST at pathology review, and had no overt metastases at study entry

Patients with a new cancer or a cardiac event

Event	Imatinib for 1 yr	Imatinib for 3 yrs	All patients
	No. (%) ¹	No. (%)	No. (%)
Any new cancer	24 (12)	34 (17)	58 (15)
Prostate cancer ²	7 (4)	7 (4)	14 (4)
Cardiac event	12 (6)	10 (5)	22 (6)
Myocardial infarction	3 (2)	3 (2)	6 (2)
Cardiac failure	1 (1)	1 (0)	1 (0)

¹Five patients in the 1-year group were unevaluable for cardiac events

²Prostate cancer was the most commonly detected cancer followed by basal cell cancer of the skin and melanoma

Conclusions

- Three years of adjuvant imatinib is superior in efficacy (RFS and OS) as compared to 1 year of imatinib
- About 50% of deaths can be avoided during the first 10 years of follow-up after surgery with the longer adjuvant imatinib treatment

Standard

- Evaluation of risk of recurrence
- Imatinib 400 mg for 3 years in case of significant risk
- No adjuvant therapy in low risk patients
- Mutation analysis is mandatory
- No adjuvant therapy in PDGFRA Exon 18 D842V
- No adjuvant therapy in Kit/PDGFRA wild type