Relevance of molecular markers for management of GIST tumors

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Disclosures

Research / Travel Support / Ad Boards;

- Novartis
- Pfizer
- Bayer

Relevance of molecular markers for management of GIST tumors?

- Not all centres have access to molecular testing
- The treatment is the same whether you know the mutation status or not
- Treatment changes are the same whether you know the mutation status or not.
- Secondary resistance is multifactorial and when due to secondary mutations is almost always treated in the same manner

GIST Diagnosis -Immunohistochemistry

- KIT protein (CD117): positive in 95% of cases
- DOG1: positive in >95% of KIT-positive GIST and 35% of KIT-negative GIST
- CD34: positive in 70-80% of cases
- Smooth muscle actin (SMA): variably positive in 40% of cases
- Desmin: generally negative
  - Expressed in most leiomyosarcomas
- PKC θ: may be helpful for the identification of KIT-negative GIST
- Carbonic anhydrase-II (CA-II): overexpressed in GIST*

Courtesy of J. Fletcher. Presented at: Global Interdisciplinary Specialists Training Around the World (GISTour) 2009. 22 November 2009, Taipei, Taiwan.

* Parkkila S et al. Mod Pathol. 2010 Jan 15. [Epub ahead of print]

The role of genetic changes in GIST

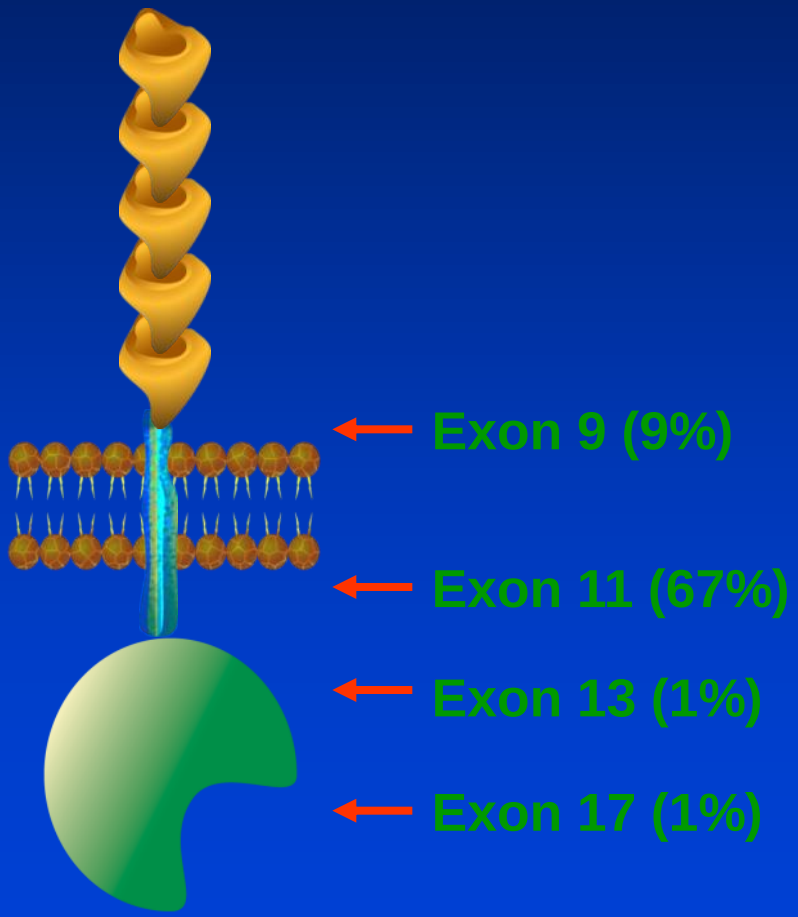
Mutations

- ~85% of GISTs have mutations in *KIT* or *PDGFRA* genes
- Mutations occur early in the development of GIST
  - Incidental tumours ≤1 cm have *c-KIT* mutations
  - Germline *c-KIT* mutations are associated with multiple GISTs
  - Cytogenetic changes in GIST are preceded by *c-KIT* mutations

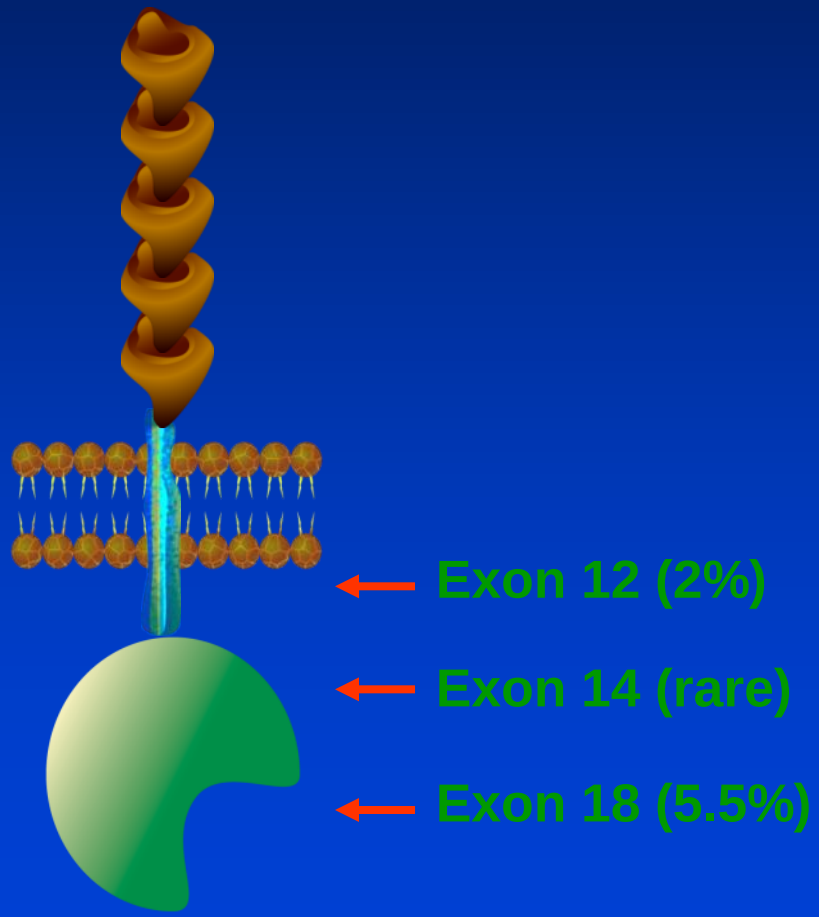
Manley et al. Eur J Cancer. 2002;38 (suppl 5):S19-S27.
Heinrich et al. Hum Pathol. 2002;33:484-495.

KIT and PDGFRA Mutations:
Overall Mutation Frequency 86%

KIT (78.5%)

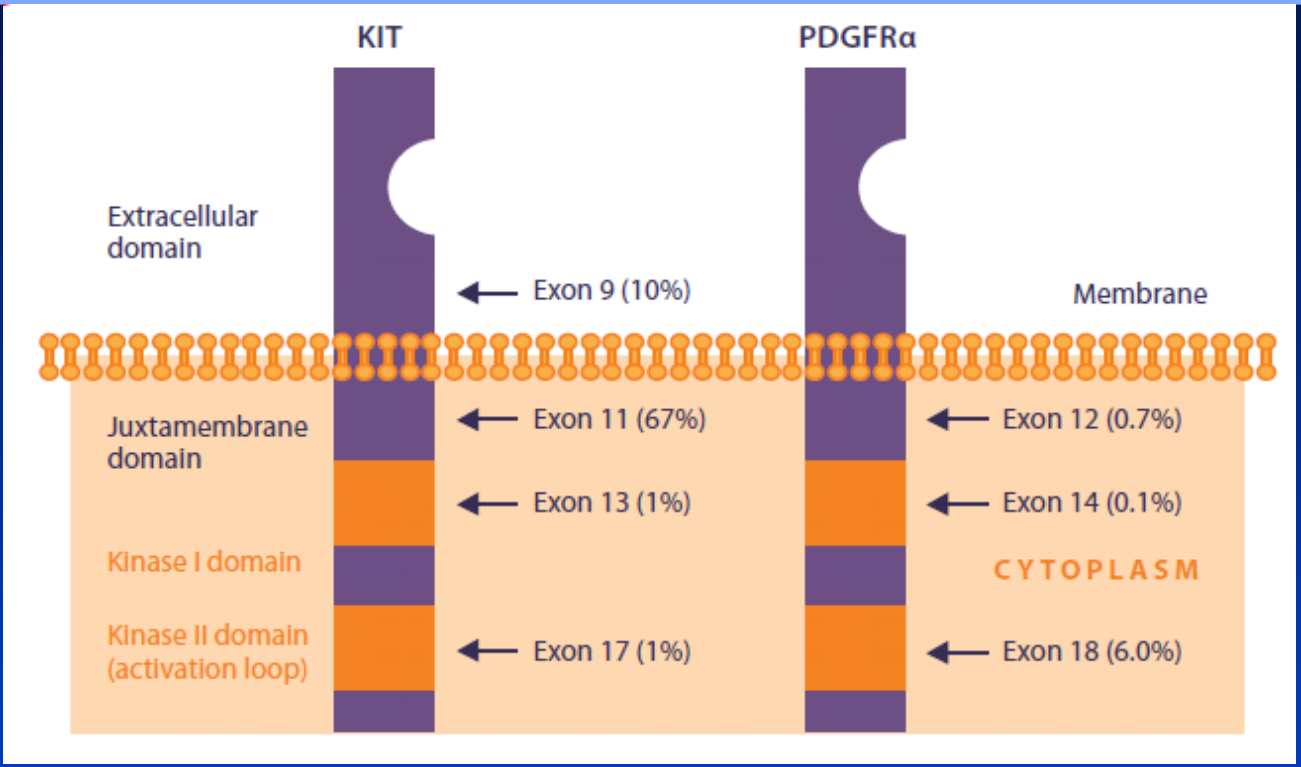


PDGFRA (7.5% total)



Corless & Heinrich. Ann Rev Pathol. 2008;3:557-586.

KIT and PDGFRα Tyrosine Kinases: Structure



- KIT and PDGFRα are:
  - Highly homologous proteins of the type III receptor tyrosine kinase family
  - Involved in signal transduction in a range of cell functions, including proliferation, differentiation, apoptosis, survival, and adhesion

Corless CL, Heinrich MC. *Annu Rev Pathol* 2008;3:557–586.

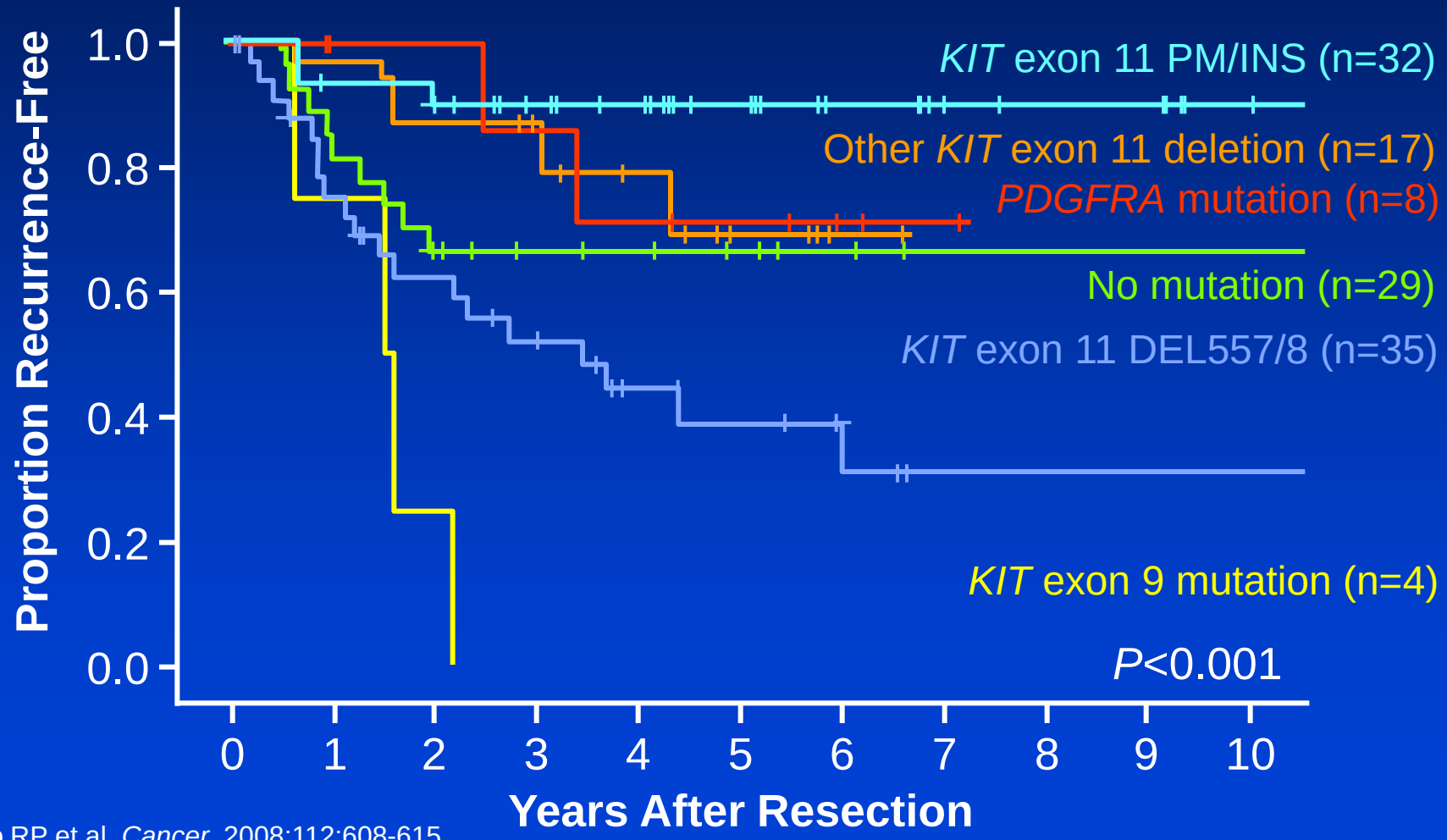
Wild-Type GIST (No KIT or PDGFRA Mutation)

Alteration	Estimated Frequency	References
BRAF mutation	< 7%	Agaram et al. Genes Chromosomes Cancer. 2008;47(10):853-859
KRAS 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*	~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	High	Janeway et al. PNAS. 2011;108(1):314-318
Germline NF1 mutation	Rare	Andersson et al. Am J Surg Pathol. 2005; 29:1170-1176

*Carney-Stratakis syndrome: association of GIST and paraganglioma

Specific KIT Mutations Have Prognostic Importance

RFS in 127 patients with completely resected localized GIST based on mutation type



DeMatteo RP et al. *Cancer*. 2008;112:608-615.

Risk Stratification of Primary GIST: Miettinen (AFIP)

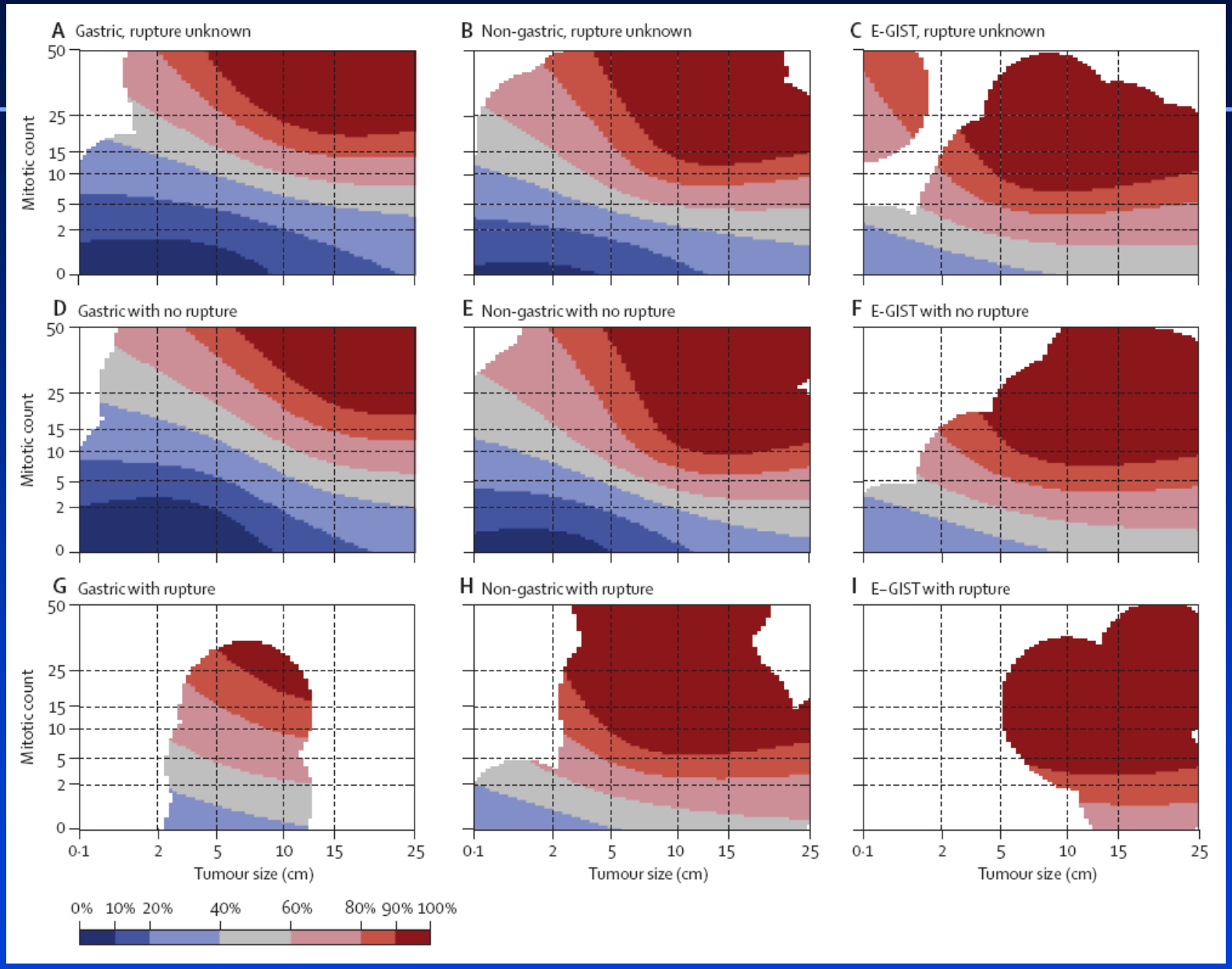
RISK FOR PROGRESSIVE DISEASE (metastasis or tumour-related death)
By mitotic count, tumour size, and tumour site

MITOTIC INDEX (High power field)	TUMOUR SIZE (cm)	GASTRIC	JEJUNUM/ ILEUM	DUODENUM	RECTUM
≤5/50	≤2	0% (None)	0% (None)	0% (None)	0% (None)
	>2 ≤5	1.9% (Very low)	4.3% (Low)	8.3% (Low)	8.5% (Low)
	>5 ≤10	3.6% (Low)	24% (Moderate)	34% (High)≈	57%† (High)≈
	>10	12% (Moderate)	52% (High)		
>5/50	≤2	0%†	50%† (High)	Not Determined∂	54% (High)
	>2 ≤5	16% (Moderate)	73% (High)	50% (High)	52% (High)
	>5 ≤10	55% (High)	85% (High)	86% (High)≈	71% (High)≈
	>10	86% (High)	90% (High)		

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.

† Denotes small numbers of cases.
≈ Tumour size categories combined for both duodenal and rectal GISTs because of small numbers.
∂ No tumours of such category were included in this study.

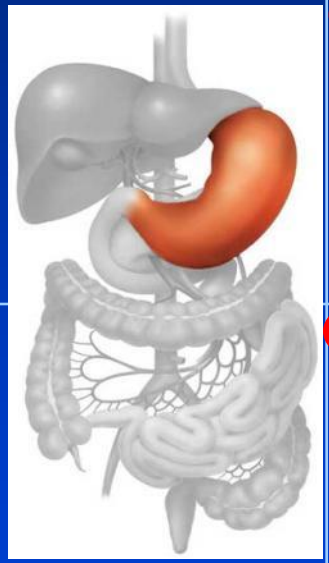
Original source: Miettinen M, Lasota J. *Semin Diagn Pathol.* 2006;23:70-83.

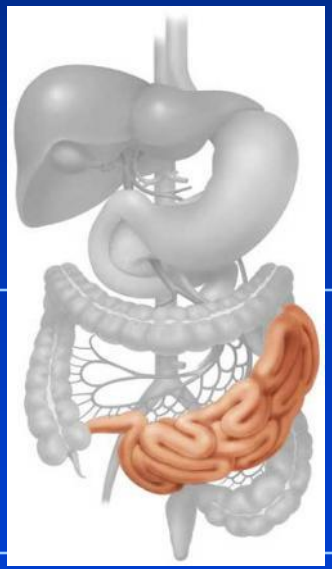


Joensuu H et al. Lancet Oncol, 13; 265-274, 2012

Mutation Subtypes According to the Primary Location

Genotype	Stomach (n=738)	Small bowel (n=261)
KIT mutation	65.2%	79.7%
Exon 9	1.8%	23%
Exon 11	61.4%	54%
Exon 13	1.2%	2.3%
Exon 17	0.8%	0.4%
PDGFRA mutation	22.9%	1.2%
Exon 12	3.1%	0%
Exon 14	0.5%	0.4%
Exon 18	19.3%	0.8%
Wild type	11.9%	19.1%



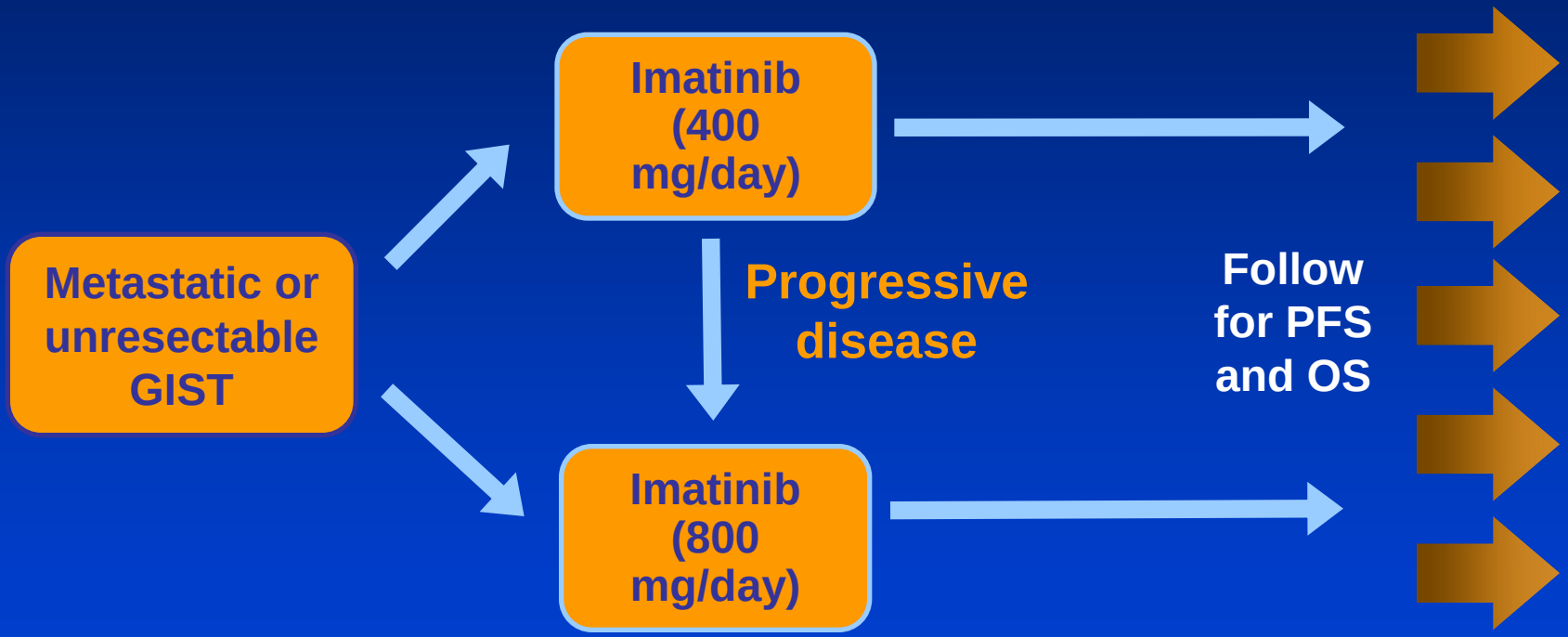


Wardelmann et al. *Pathologe* 2010 epub ahead of print

Impact of mutation status on treatment

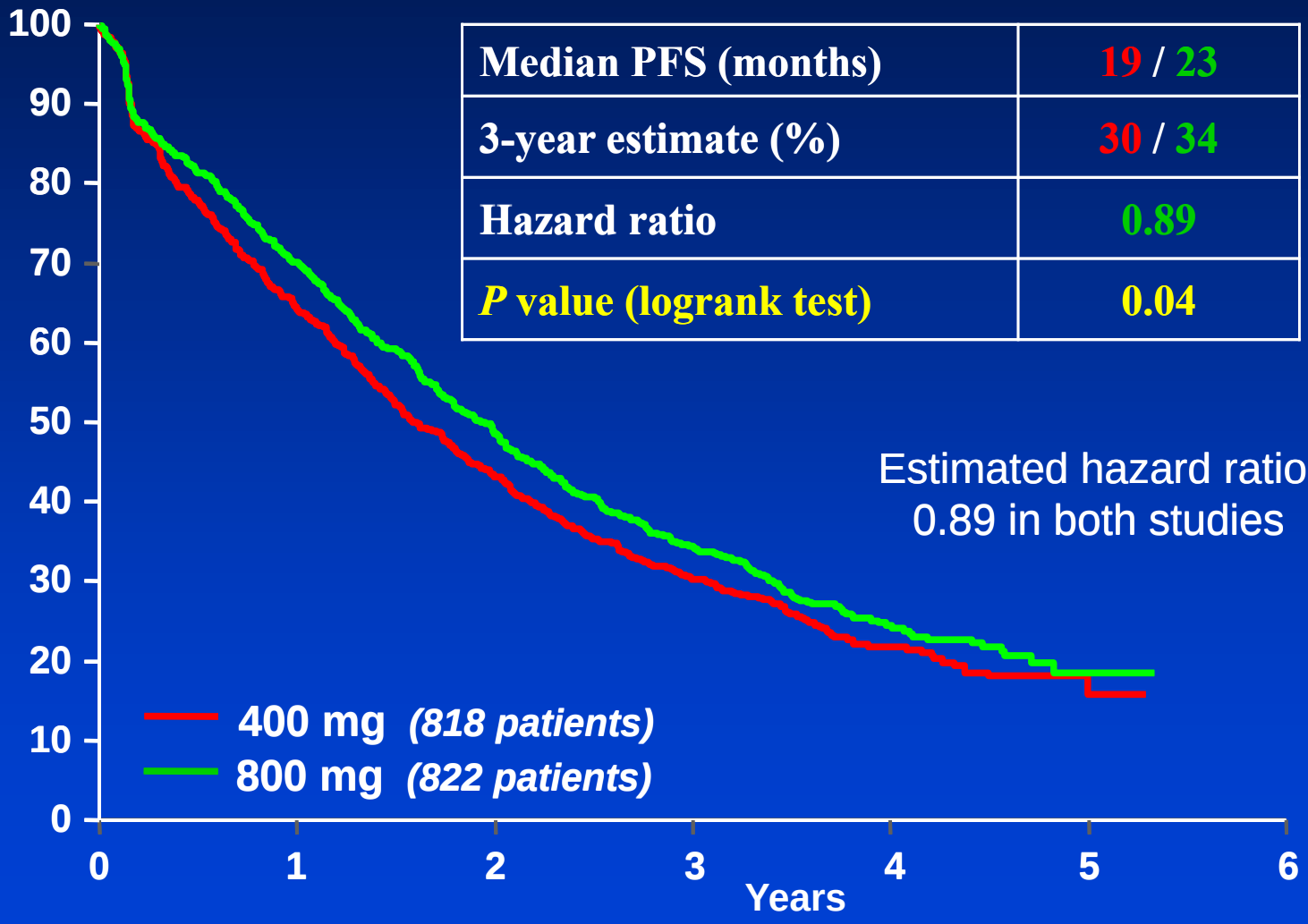
MetaGIST; Analysis of High and Low Imatinib Doses: Design of Trials

EORTC/ISG/AGITG Study 62005[1]
North American Intergroup Study S0033[2]



1. Verweij J, *et al*. *Lancet* 2004;364:1127–1134.
2. Blanke CD, *et al*. *J Clin Oncol* 2008;26:626–632.

Progression Free Survival: Entire MetaGIST Population

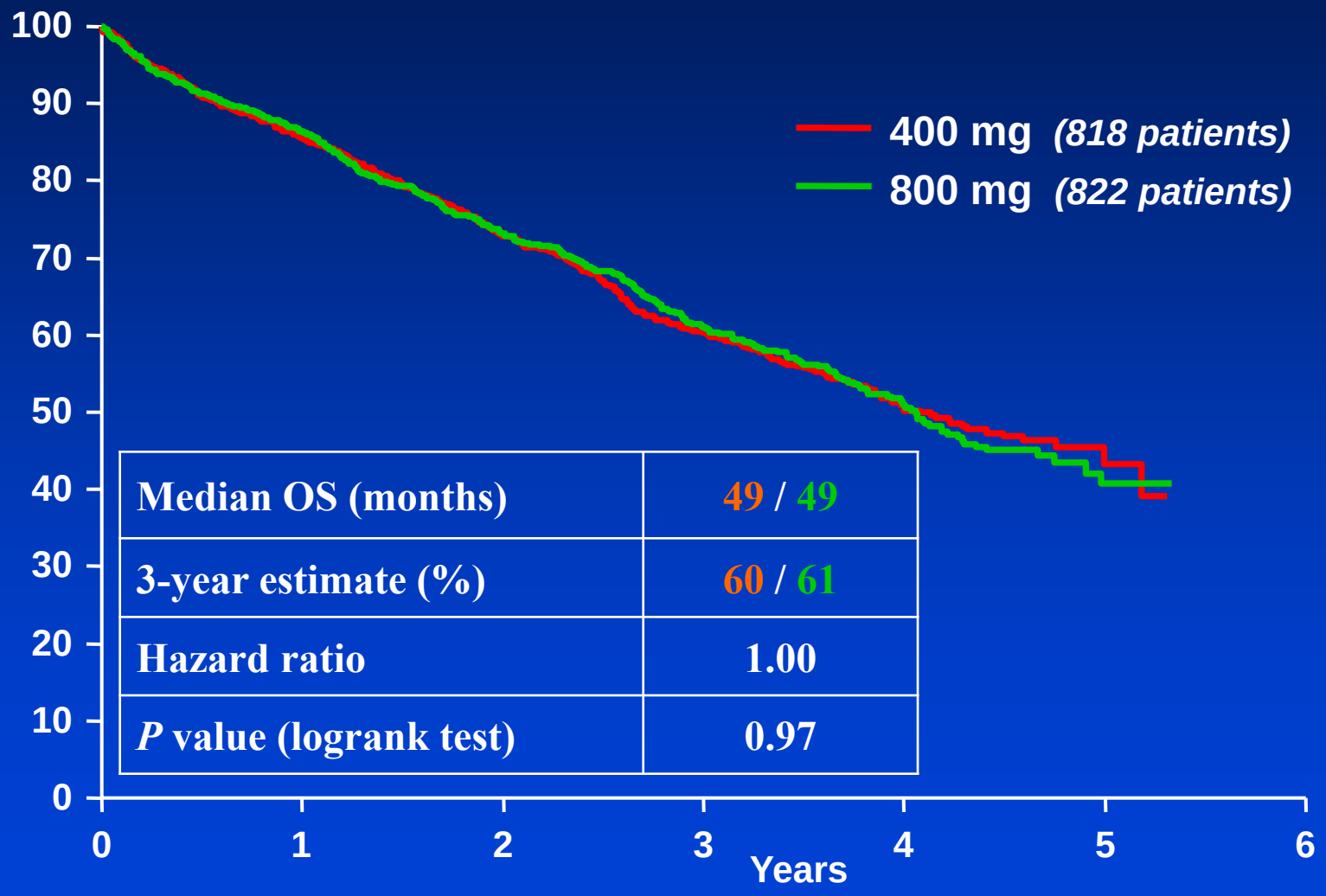


Median PFS (months)	19 / 23
3-year estimate (%)	30 / 34
Hazard ratio	0.89
P value (logrank test)	0.04

Estimated hazard ratio:
0.89 in both studies

Van Glabbeke et al. ASCO 2007. Abstract 10004.

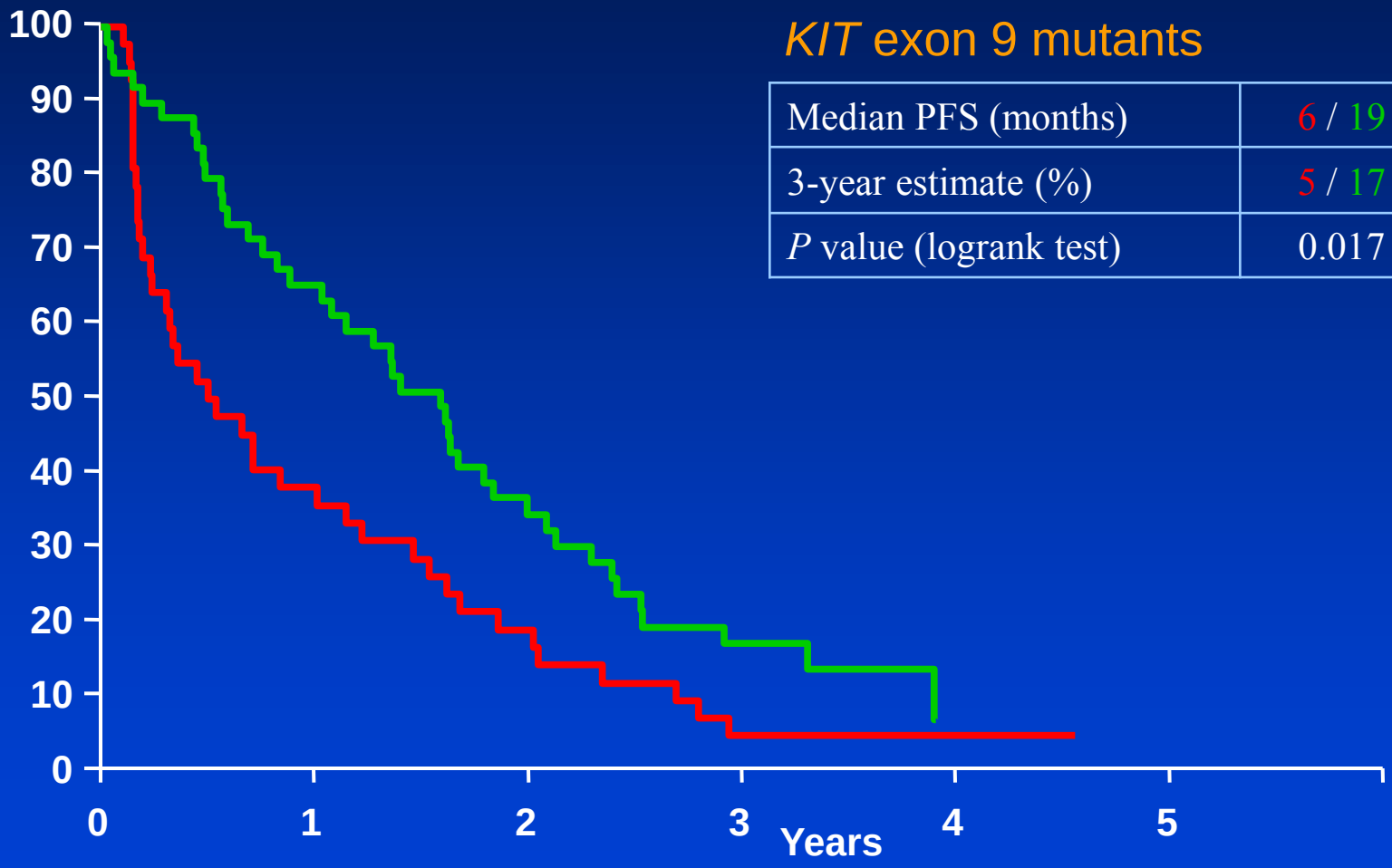
MetaGIST: Overall Survival



Median OS (months)	49 / 49
3-year estimate (%)	60 / 61
Hazard ratio	1.00
P value (logrank test)	0.97

Van Glabbeke et al. ASCO 2007. Abstract 10004.

MetaGIST: Progression Free Survival (KIT exon 9)



KIT exon 9 mutants

Median PFS (months)	6 / 19
3-year estimate (%)	5 / 17
P value (logrank test)	0.017

KIT exon 9 mutants: 400 mg / 800 mg

Van Glabbeke et al. ASCO 2007. Abstract 10004.

MetaGIST Analysis: Impact of Imatinib Dose on PFS by *KIT* Exon 9 Mutation Status

Treatment	N	*P*-value Log Rank	HR (Adjusted) (95% CI)	HR (Non-adjusted) (95% CI)	*P*-value Interaction Test
Patients with *KIT* exon 9 mutations					0.012
400 mg	42	0.0171	0.58 (0.38, 0.91)	0.57 (0.37, 0.89)	
800 mg	49				
Patients without *KIT* exon 9 mutations					
400 mg	341	0.8586	1.02 (0.85, 1.21)	1.02 (0.86, 1.22)	
800 mg	340				

van Glabbeke MM, *et al. J Clin Oncol*.DOI.10.1200./JCO.2009.24. 2099.

Imatinib Resistance in GIST

- 14% of GIST patients exhibit primary resistance: i.e. early tumor progression (within 6 months of beginning imatinib therapy)
- 50% of all GIST patients exhibit tumor progression within 2 years of starting imatinib therapy i.e. secondary resistance

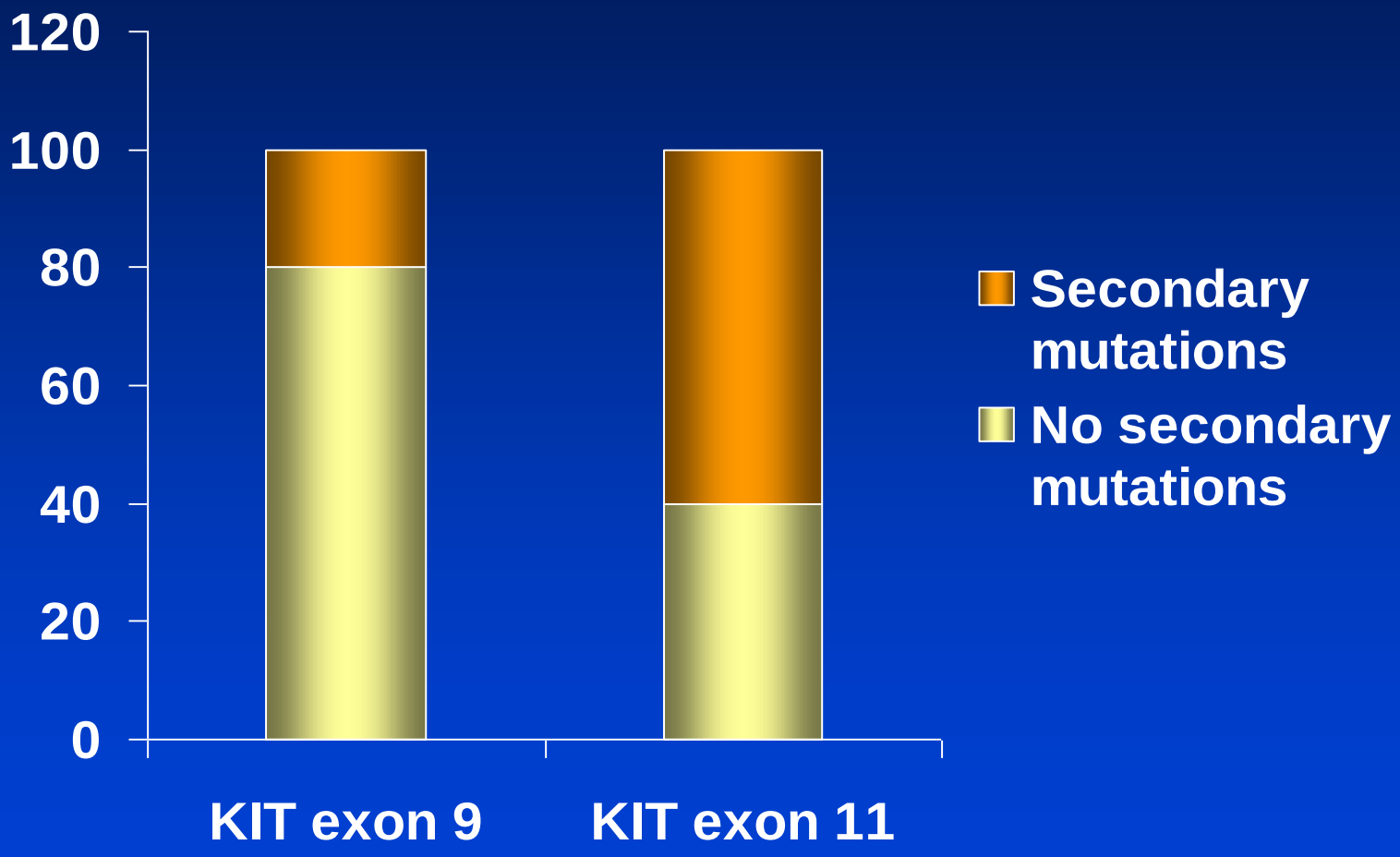
Demetri et al. N Engl J Med. 2002;347:472-480.
Verweij et al. Lancet. 2004;364:1127-1137.

Mechanisms of Imatinib Resistance

- Primary imatinib resistance is more common in GISTs with the following genotypes
  - *KIT* exon 9 mutations
  - *PDGFRA* D842V mutations
  - No detectable mutations (WT *KIT/PDGFRA* genotype)
- Secondary imatinib resistance is commonly associated with the emergence of new kinase mutations

Antonescu et al. Clin Cancer Res. 2005;11:4182-4190.
Heinrich et al. J Clin Oncol. 2003;21:4342-4349.
Debiec-Rycher et al. Eur J Cancer. 2006;42:1093-1103.
Heinrich et al. J Clin Oncol. 2006;29:4764-4774.

Acquired Drug Resistance



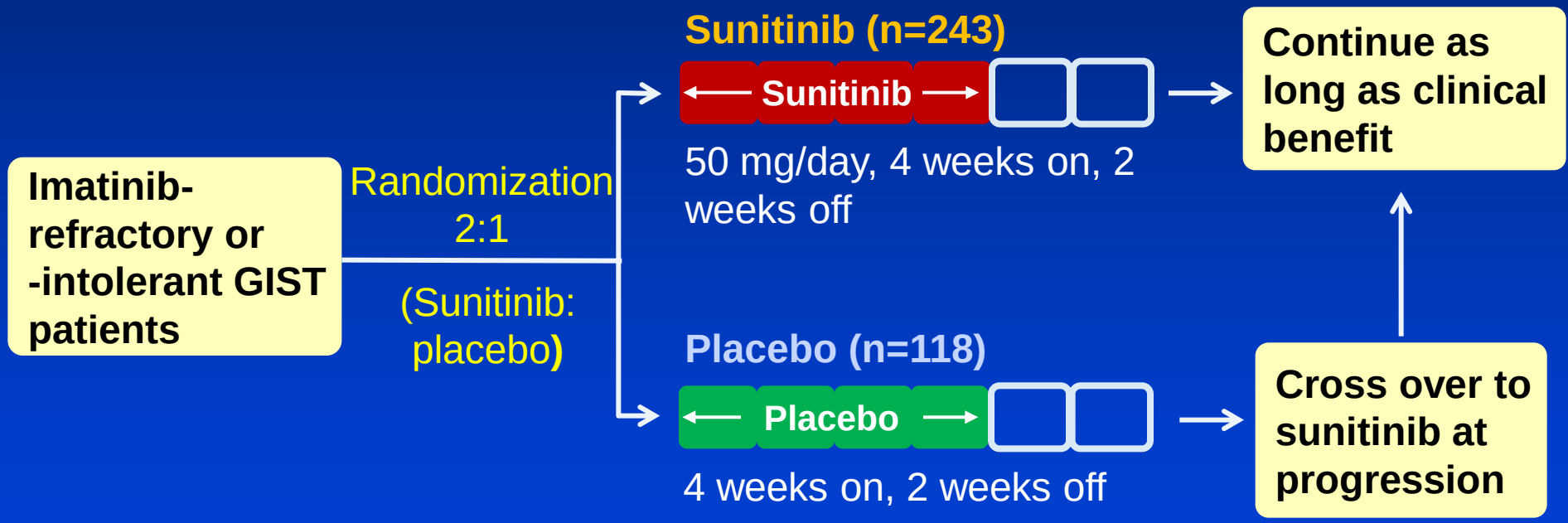
Molecular Mechanisms of Imatinib Resistance

- Mutation
  - Exon 17
  - Exon 14

  ~70%
- Target overexpression
- Substitution alternate RTK
- Activation of downstream signalling pathways

Phase 3 trial of sunitinib in imatinib-resistant/-intolerant GIST

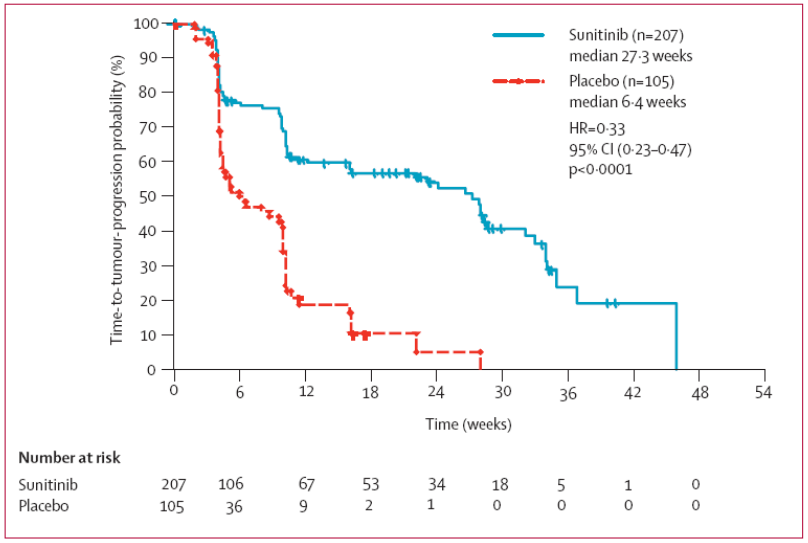
Conducted at 56 sites in Europe, USA, Australia and Asia (Singapore).
Final protocol dated August 2003

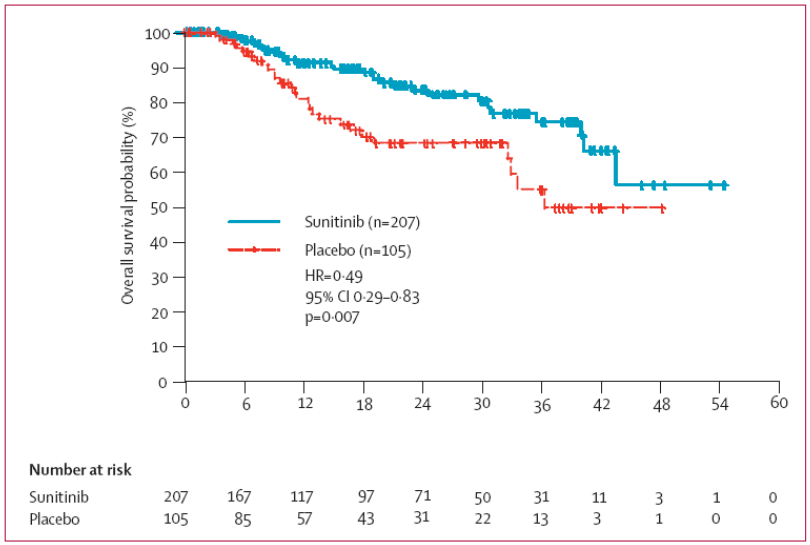


Phase III Trial: Sunitinib in Advanced GIST After Imatinib Failure

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

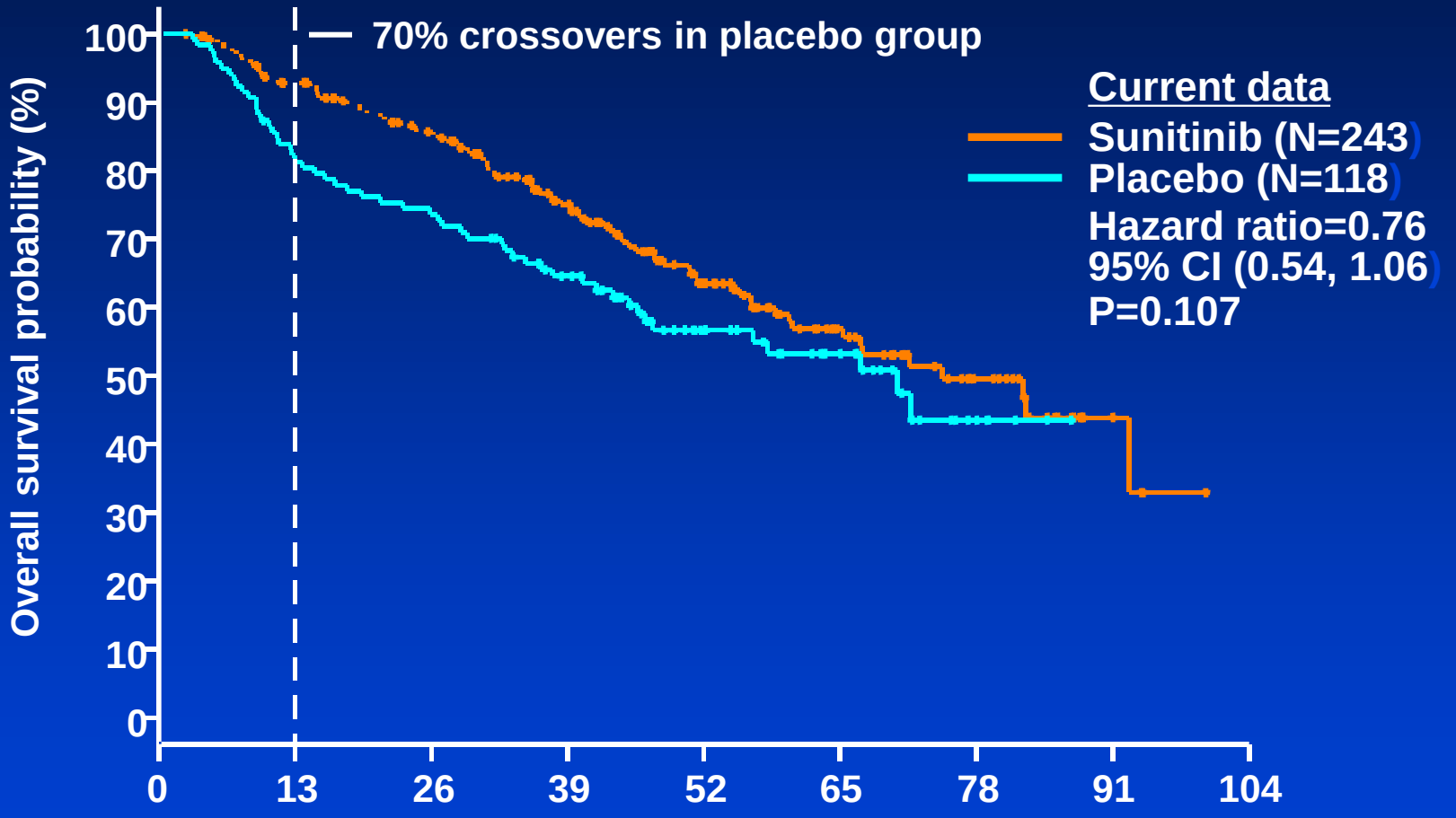
George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali



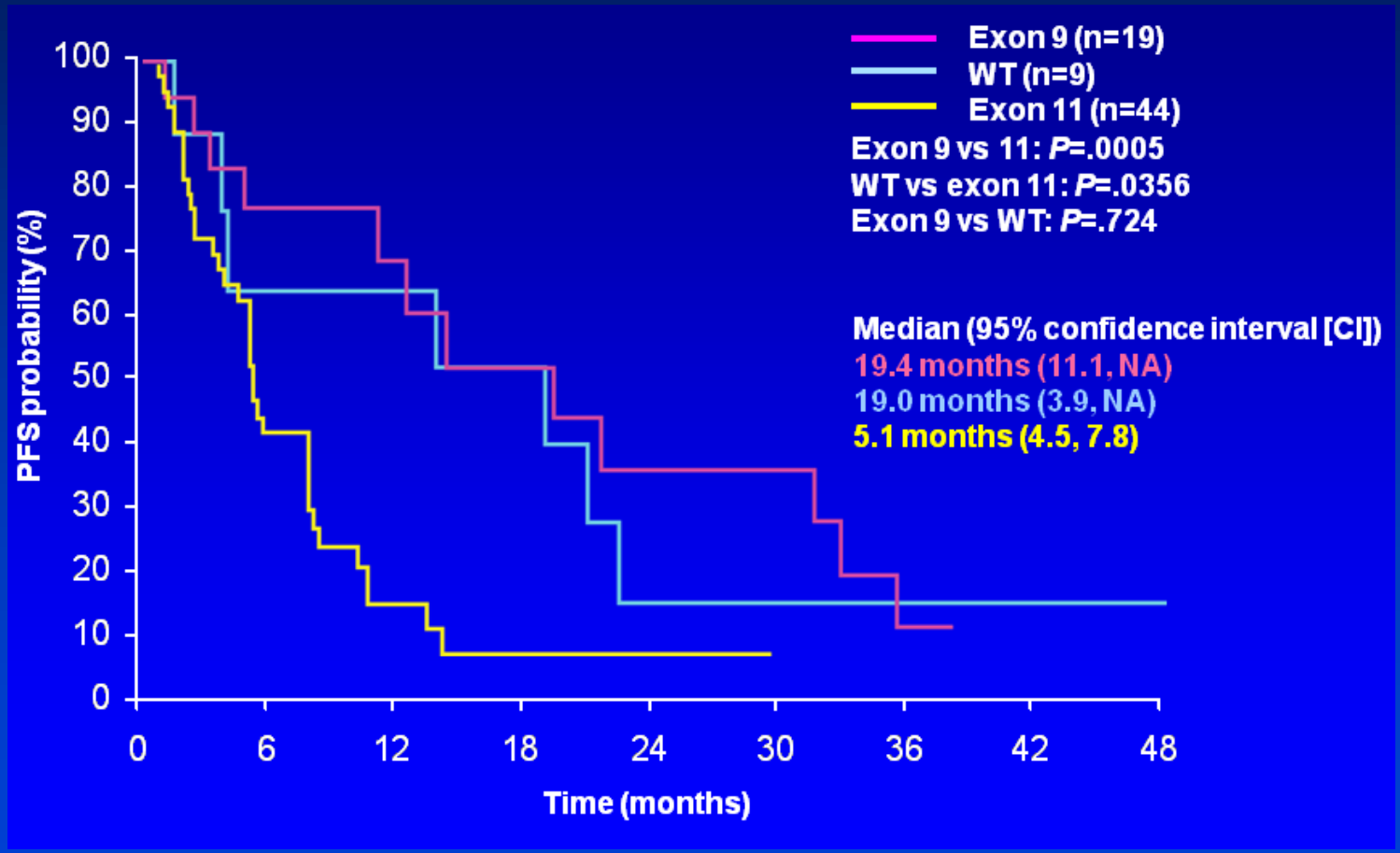


Demetri et al. Lancet. 2006;3681329-1338.

Overall Survival with Crossover to Sunitinib



Progression-Free Survival on Sunitinib in Imatinib-Resistant/Intolerant GIST



Heinrich M et al. J Clin Oncol 2008

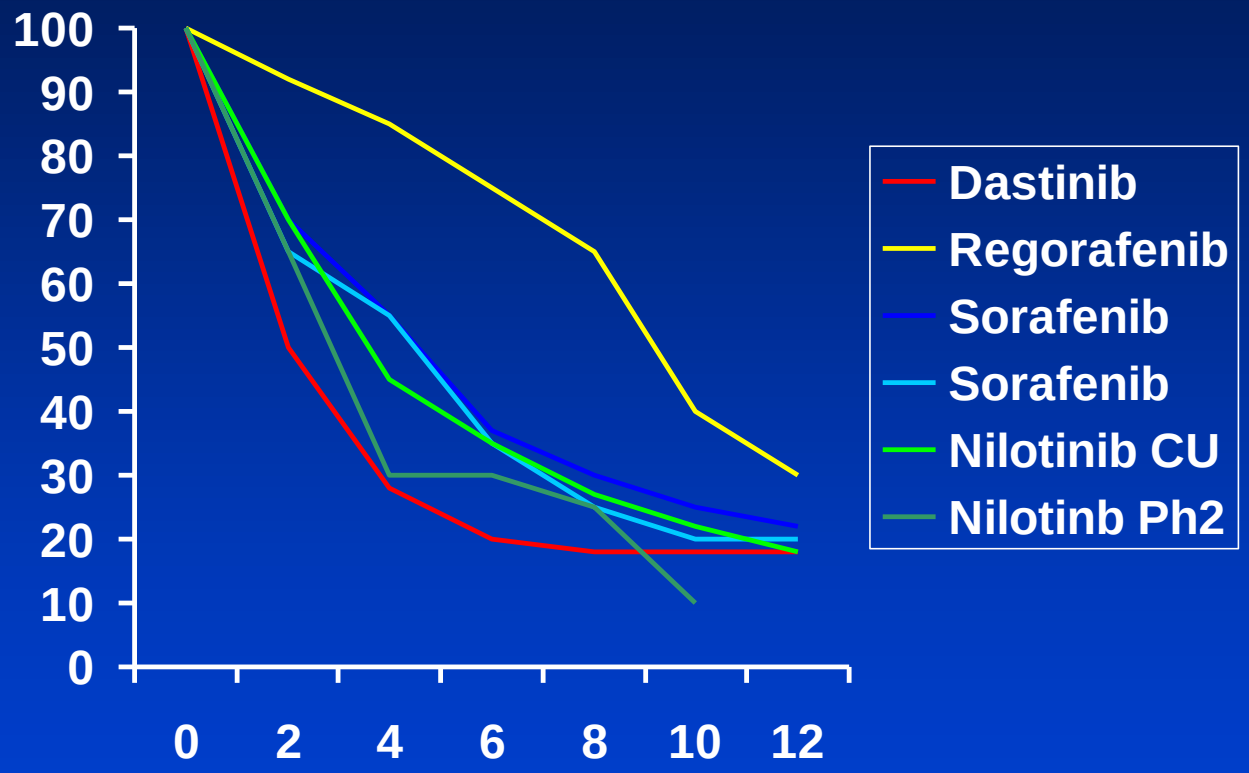
Molecular Subsets of Imatinib-Resistant GIST Highly Sensitive to Sunitinib:

Mutation Status	n	RECIST RR	Clinical Benefit (RR + SD > 6 months
Exon 9 *KIT* mutation	15	6 (40%)	12 (80%)
Single *PDGFRA* mutation	1	0	1 (100%)
Wild Type *KIT+PDGFRA*	9	1 (11%)	5 (55%)
Exon 13 or 14 as secondary mutations	16	2 (13%)	9 (56%)

Molecular Subsets of Imatinib-Resistant GIST Less Sensitive to Sunitinib:

Mutation Status	n	RECIST RR	Clinical Benefit (RR + SD > 6 months
Exon 11 *KIT* mutation	7	0	1 (14%)
Secondary Exon 17 *KIT* mutations	8	0	3 (38%)

Progression Free Survival in screening studies in 3rd line GIST

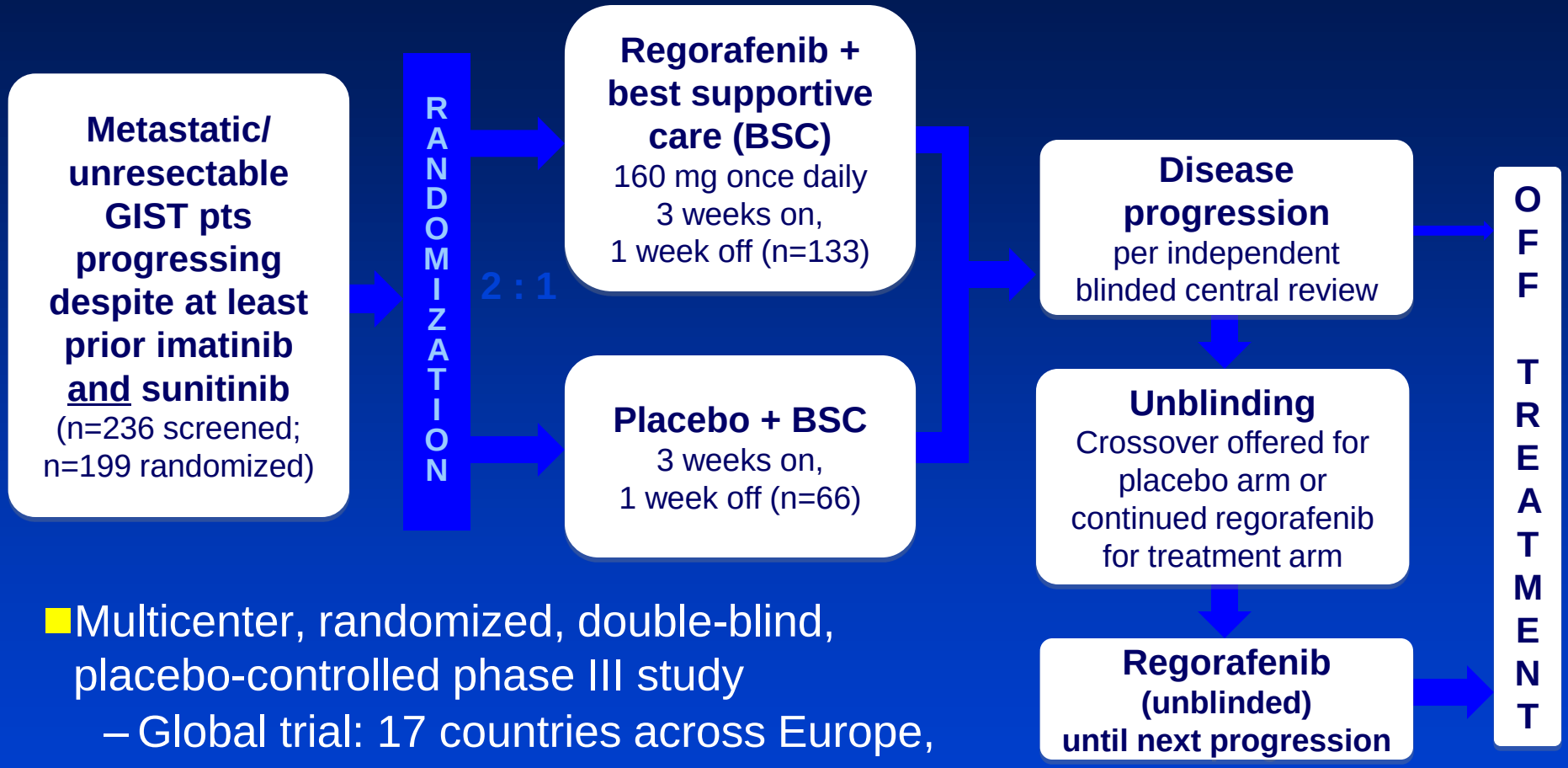


Montemurro M et al Eur.J Cancer 2009; 45:2293-2297

[2] Sawaki A et al Cancer EPUB 2011

J.Verweij, ASCO Discussion, 2011

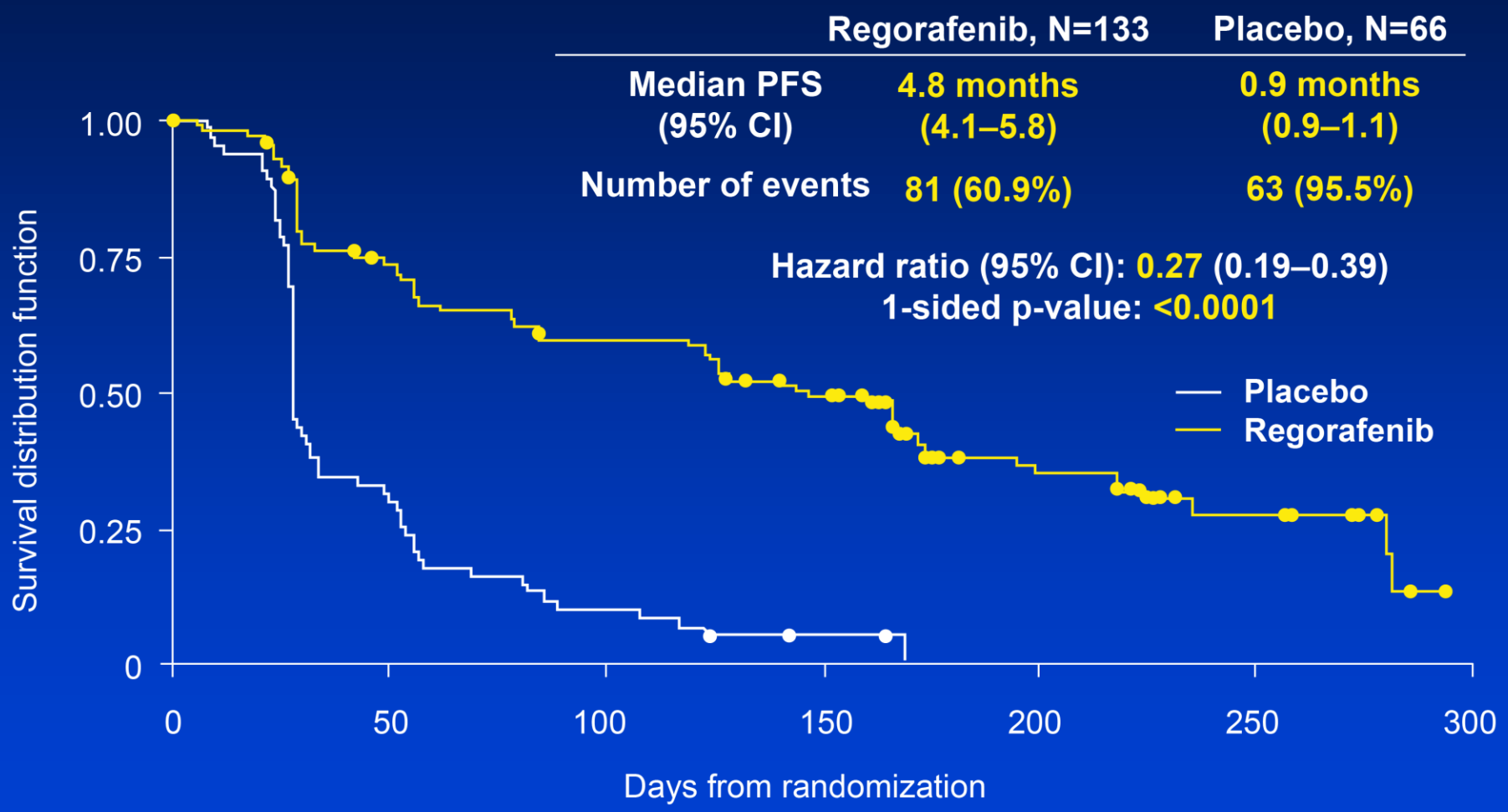
GIST – Regorafenib In Progressive Disease (GRID): Study Design



- Multicenter, randomized, double-blind, placebo-controlled phase III study
  - Global trial: 17 countries across Europe, North America, and Asia-Pacific
  - Stratification: treatment line (2 *vs* >2 prior lines), geographical location (Asia *vs* "Rest of World")

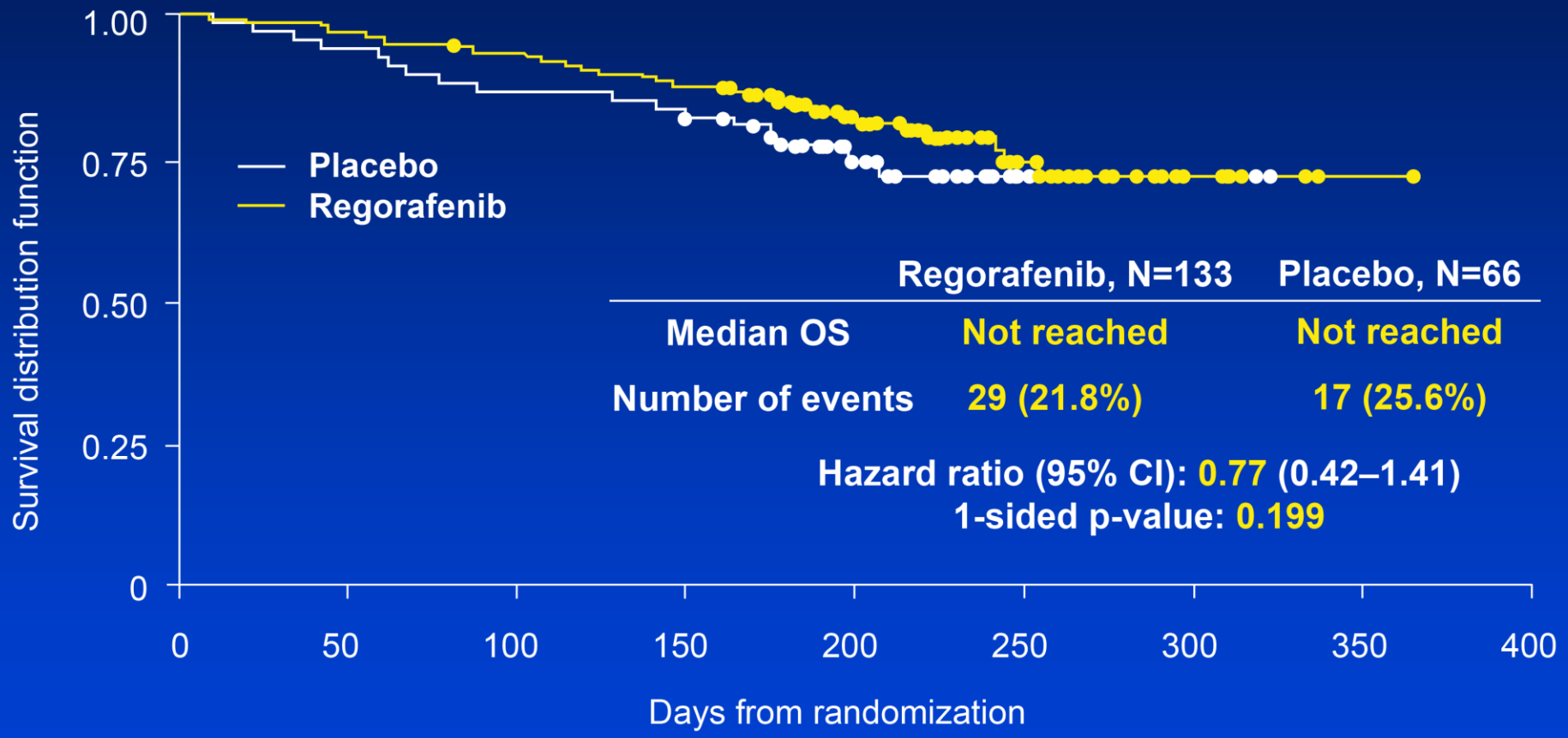
Demetri et al. ASCO 2012

GRID Study: PFS (primary endpoint per blinded central review)



Demetri et al. ASCO 2012

GRID Study: Overall Survival (following 85% cross-over of patients on placebo arm)



Demetri et al. ASCO 2012

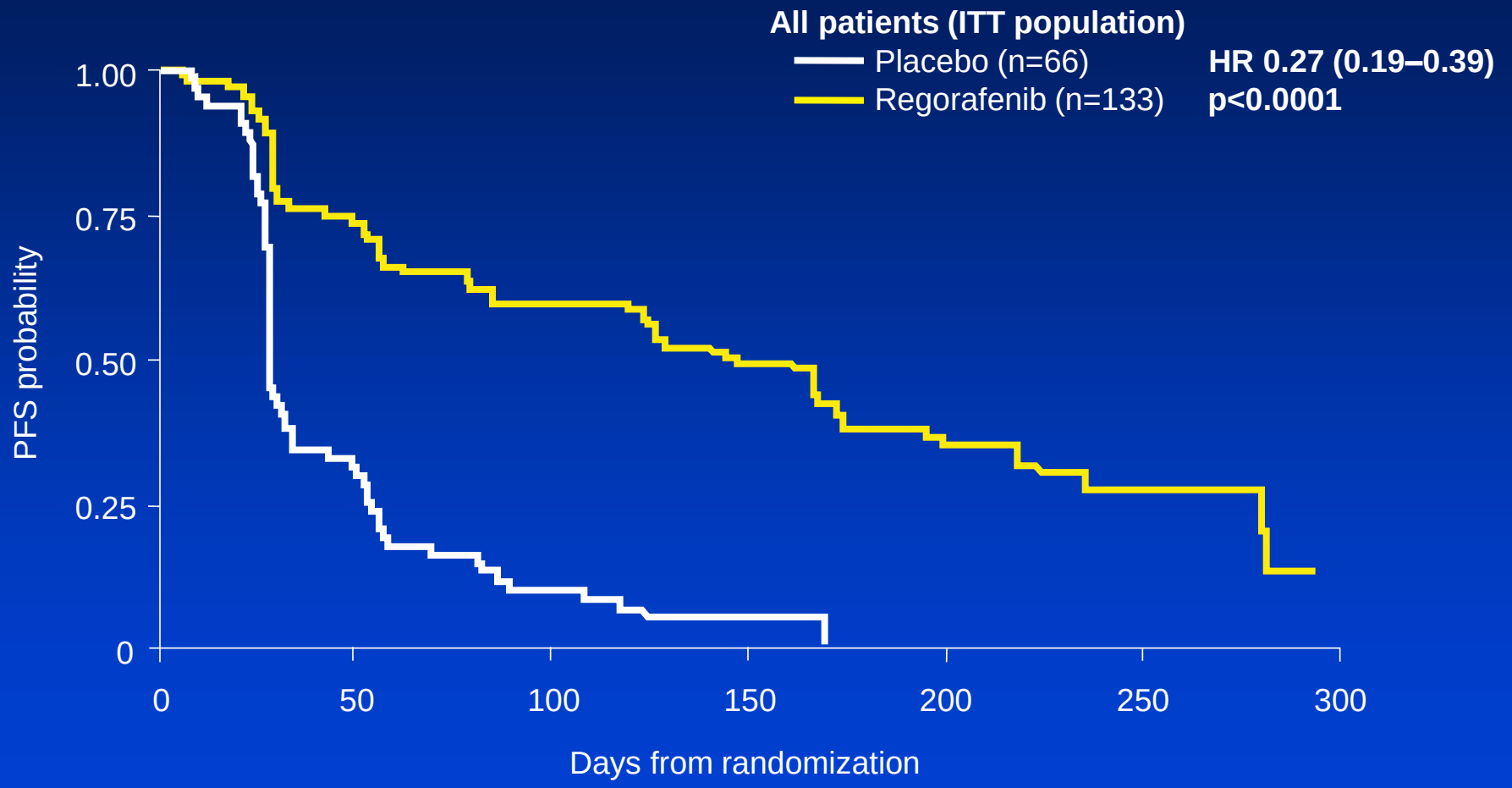
Baseline GIST Genotype per Site Reports: Exploratory Analysis of Outcomes

Tumor genotype, n (%)	Placebo	Regorafenib	Total
Prior GIST genotype available and reported at study entry (% total study population)	36 (54.5%)	60 (45.1%)	96 (48.2%)
KIT exon 11 mutation	17 (47.2%)	34 (56.7%)	51 (53.1%)
KIT exon 9 mutation	6 (16.7%)	9 (15.0%)	15 (15.6%)
Wild type *KIT* and *PDGFRA*	2 (5.6%)	6 (10.0%)	8 (8.3%)
Unspecified or other exon mutant	11 (30.5%)	11 (18.3%)	22 (22.9%)

Baseline GIST Genotype per Site Reports: Exploratory Analysis of Outcomes

Mutation biomarker	Progression-free survival				
	N	Events	HR	Placebo, median months	Regorafenib, median months
KIT exon 11	51	40	0.212	1.1	5.6
KIT exon 9 mutation	15	11	0.239	0.9	5.4

Regorafenib shows benefit over placebo in patients without secondary *KIT* mutations



ITT curves from Demetri GD *et al. Lancet* 2013; 381: 295–302

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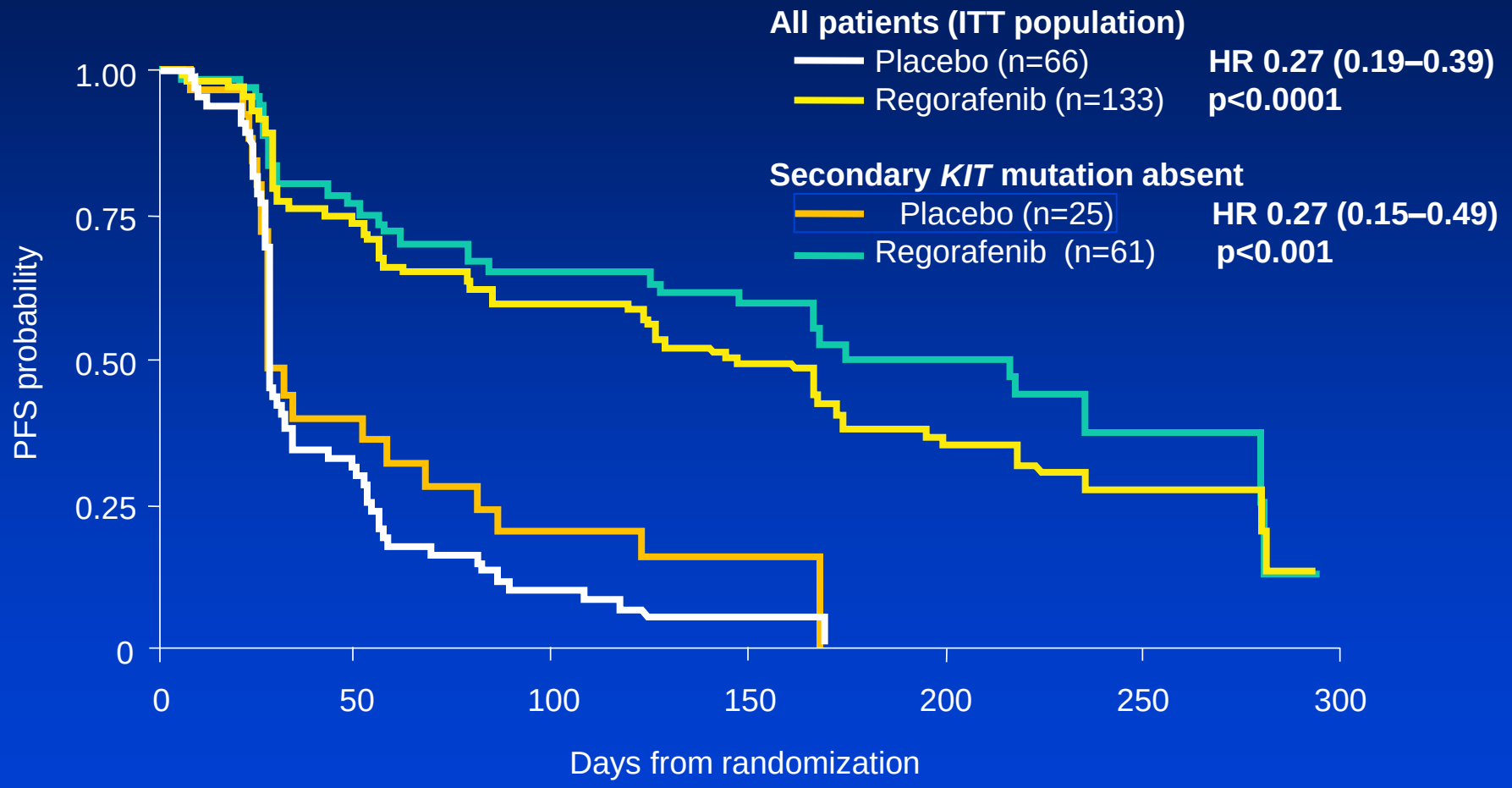

ITT curves from Demetri GD *et al. Lancet* 2013; 381: 295–302

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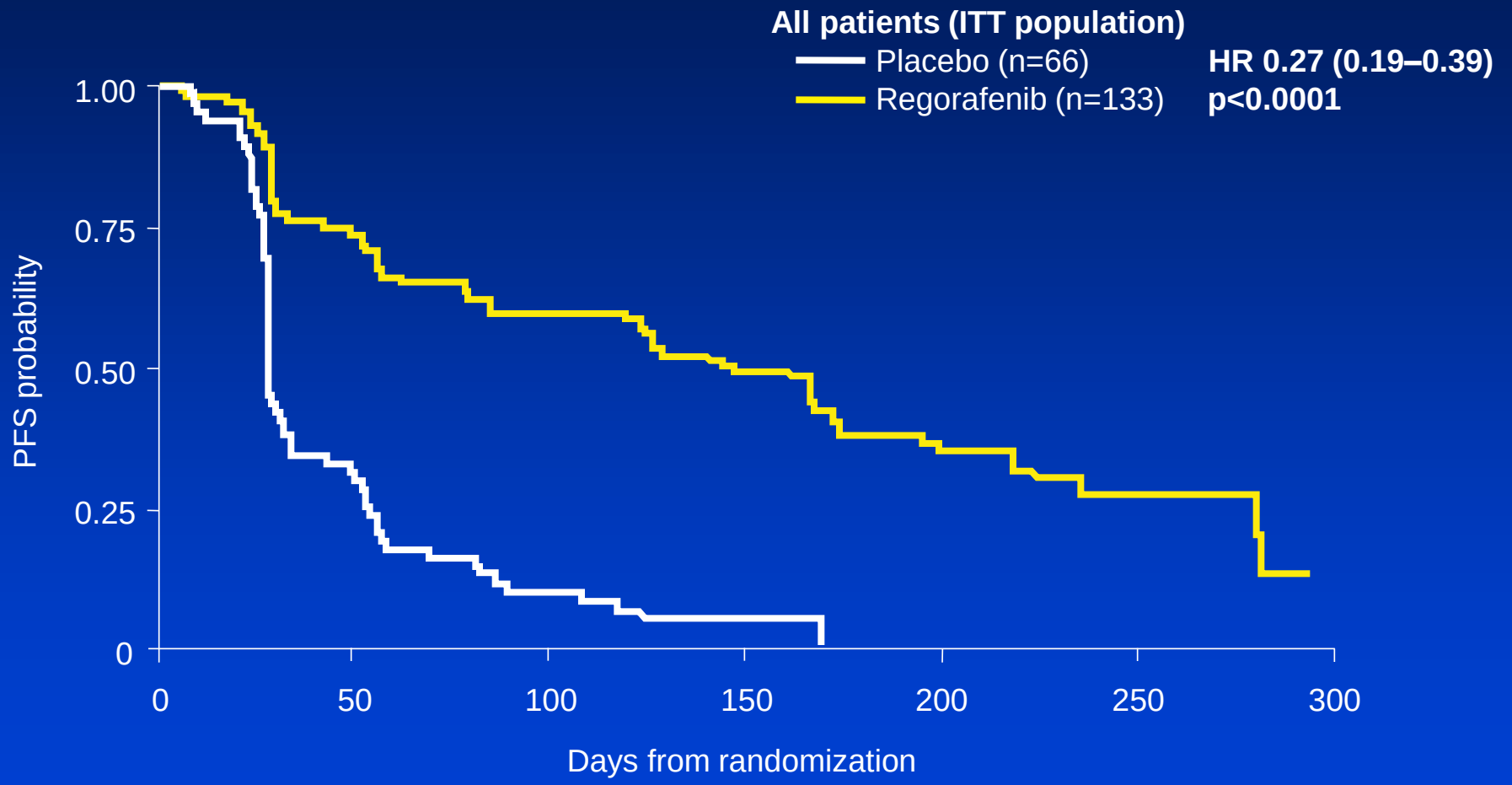

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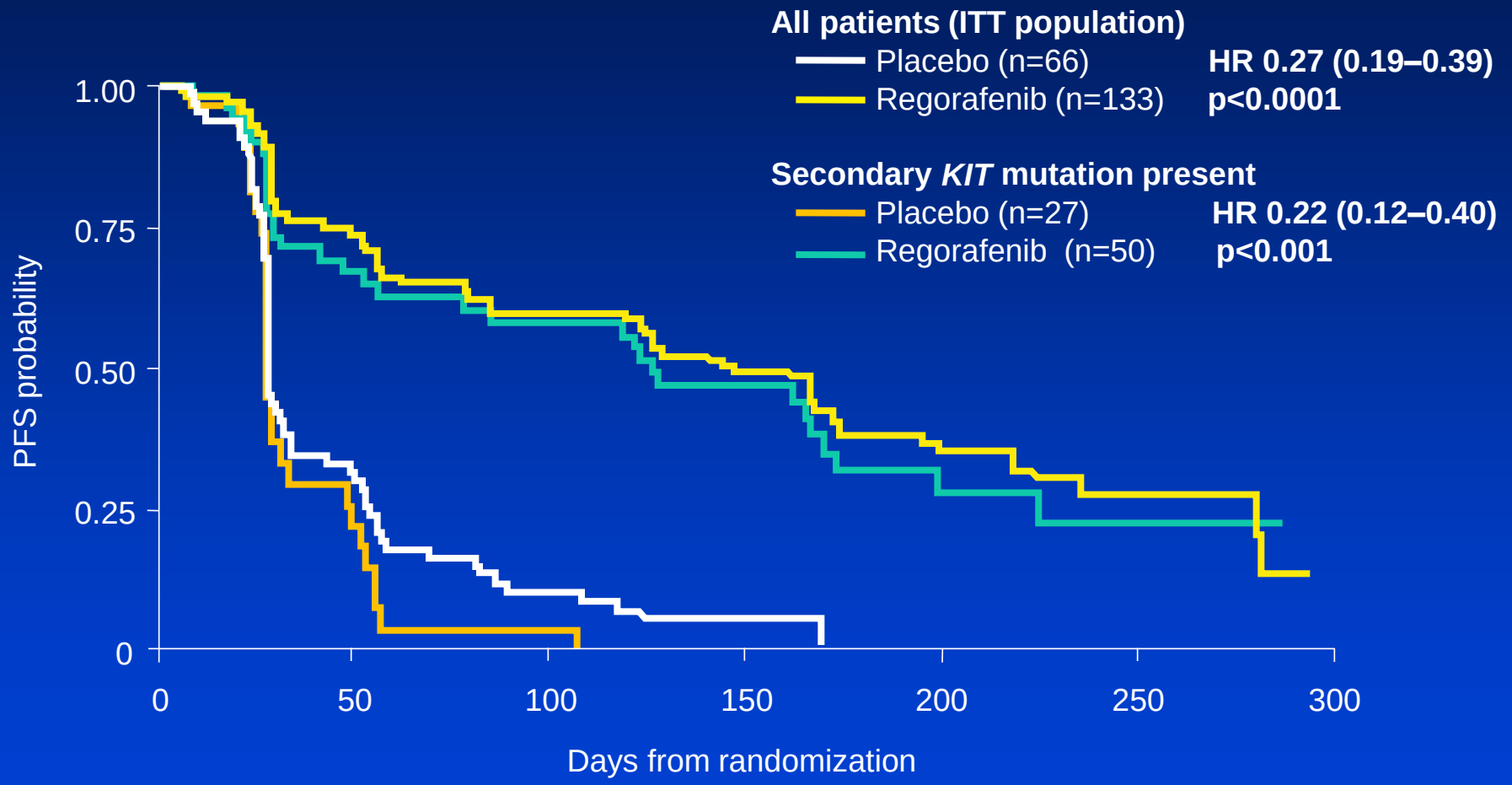
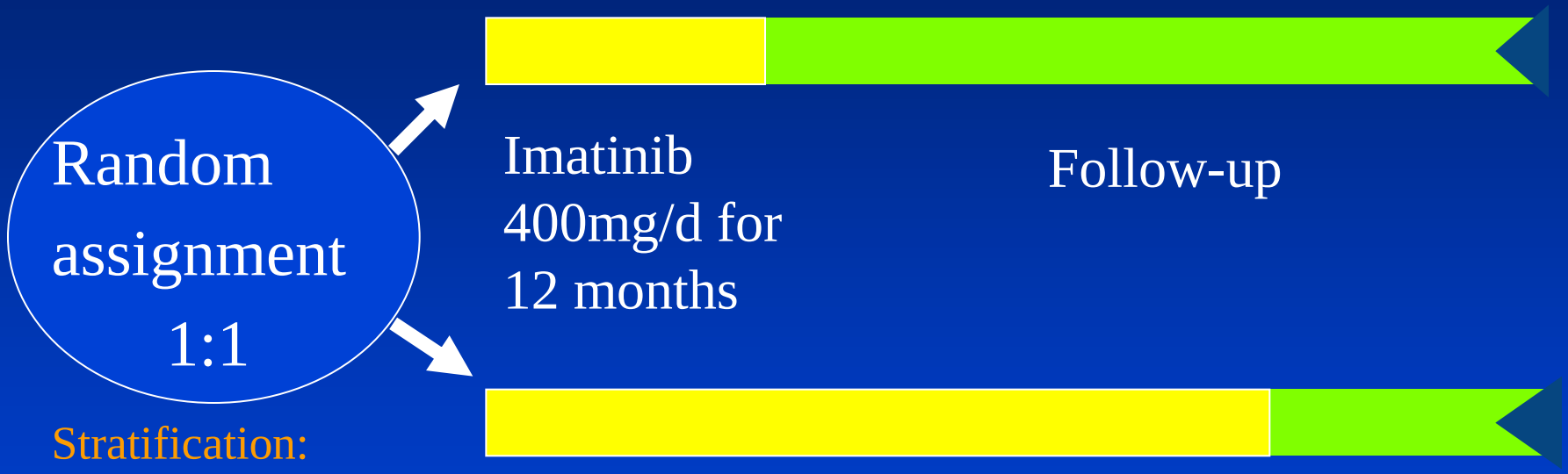


ITT curves from Demetri GD *et al. Lancet* 2013; 381: 295–302

SSGXVIII: Study design

An open-label Phase III study



Stratification:

1) R0 resection, no tumor rupture

2) R1 resection *or* tumor rupture

SSGXVIII: Objectives

- Primary: RFS
  - -Time from randomization to GIST recurrence or death

- Secondary objectives included:
  - – Safety
  - – Overall survival

SSGXIII: Key inclusion criteria

- Histologically confirmed GIST, KIT-positive
- High risk of recurrence according to the modified

  Consensus Criteria*:
  - Tumor diameter >10 cm *or*
  - Tumor mitosis count >10/50 HPF** *or*
  - Size >5 cm and mitosis count >5/50 HPFs *or*
  - Tumor rupture spontaneously or at surgery

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

**HPF, High Power Field of the microscope

Baseline characteristics (ITT)

Characteristic	12-Mo group	36-Mo group
Median age (range) - years	62 (23-84)	60 (22-81)
Male - (%)	52	49
ECOG performance status 0 - (%)	85	86
Gastric primary tumor - (%)	49	53
Median tumor size (range) - cm	9 (2-35)	10 (2-40)
Median mitosis count - /50 HPFs	10 (0-250)	8 (0-165)
Tumor rupture - (%)	18	22
GIST gene mutation site - (%)*		
- *KIT* exon 9	6	7
- *KIT* exon 11	69	71
- *KIT* exon 13	2	1
- *PDGFRA* (D842V)	13 (10)	12 (8)
- wild type	10	8

*Available for 366 (92%) out of the 397 tumors

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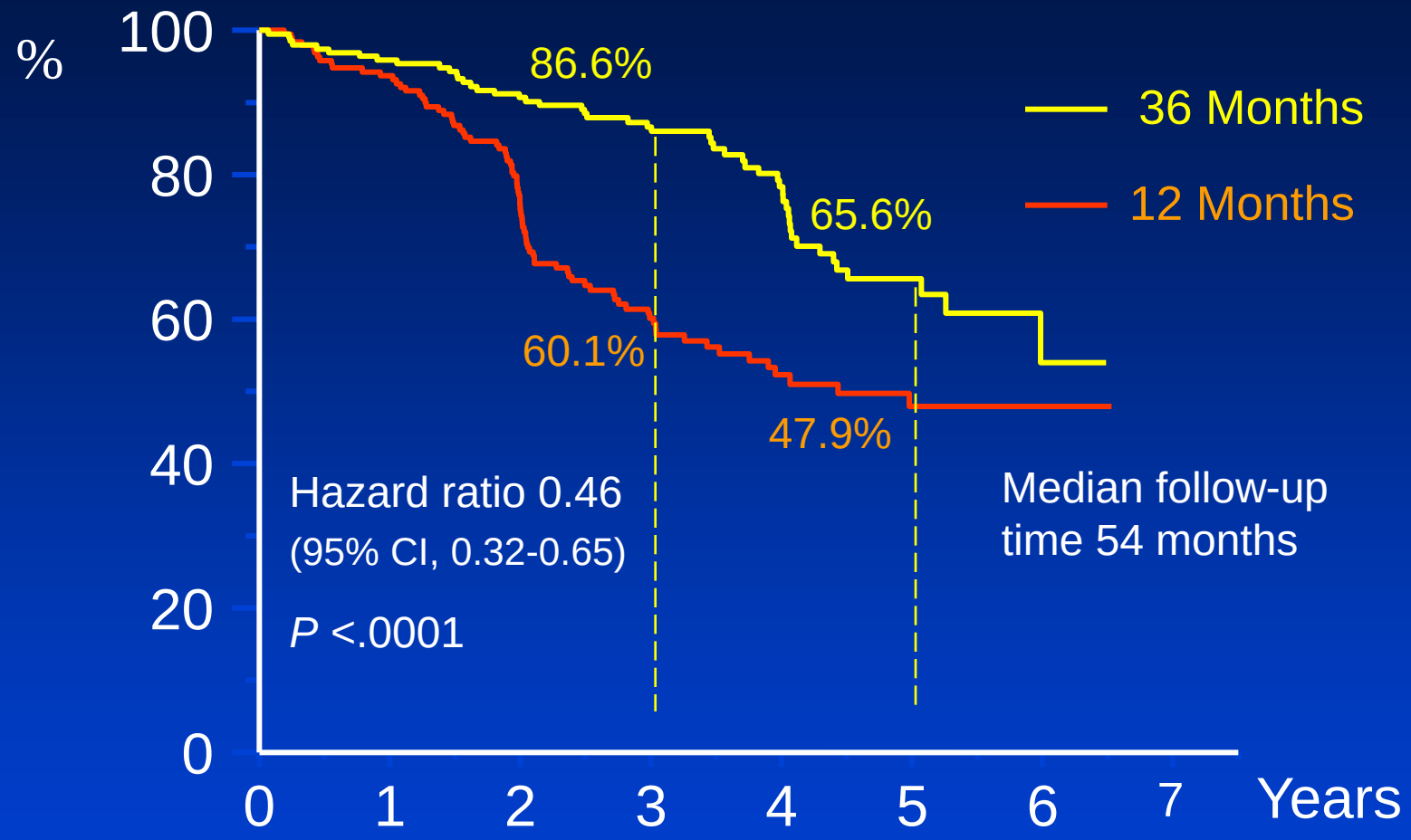
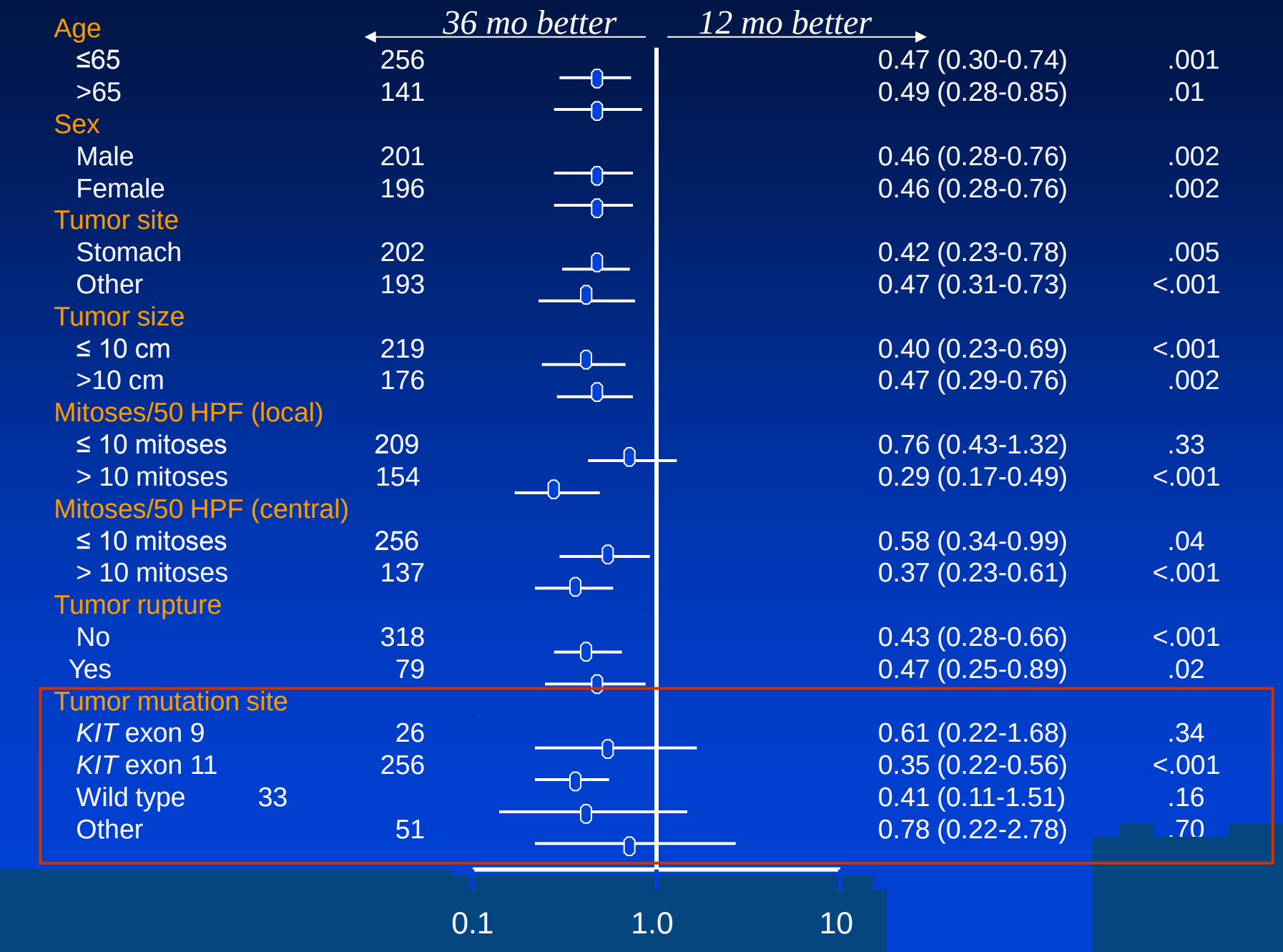
SSGXVIII: Recurrence-free survival (ITT)

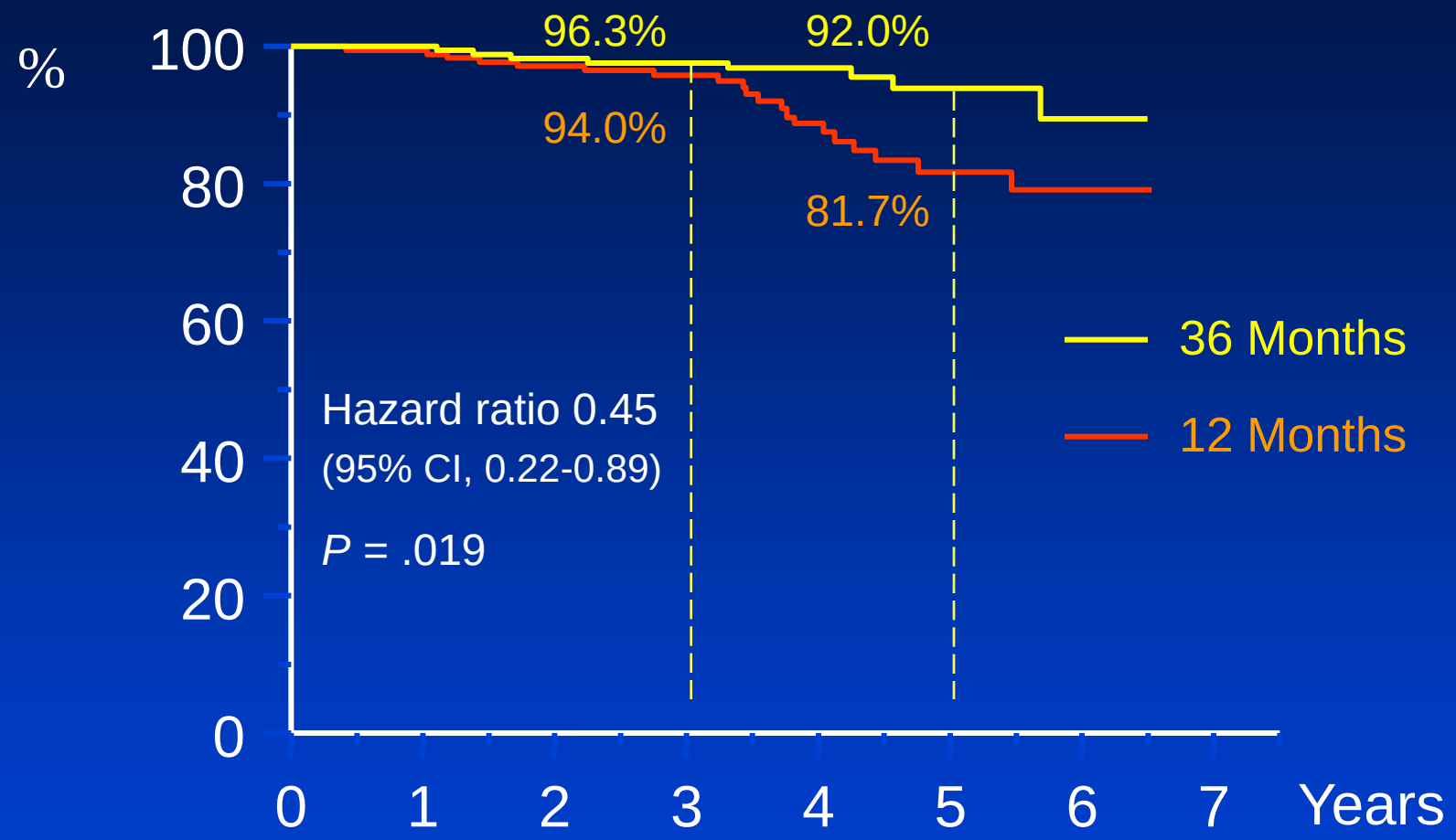


No. at risk (n=397)

36 Months of imatinib	198	184	173	133	82	39	8	0
12 Months of imatinib	199	177	137	88	49	27	10	0


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) .005
Other 193 0.47 (0.31-0.73) <.001
Tumor size
≤ 10 cm 219 0.40 (0.23-0.69) <.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 (0.17-0.49) <.001
Mitoses/50 HPF (central)
≤ 10 mitoses 256 0.58 (0.34-0.99) .04
> 10 mitoses 137 0.37 (0.23-0.61) <.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 0.61 (0.22-1.68) .34
KIT exon 11 256 0.35 (0.22-0.56) <.001
Wild type 33 0.41 (0.11-1.51) .16
Other 51 0.78 (0.22-2.78) .70
0.1
1.0
10

SSGXVIII: Overall survival (ITT)



No. at risk (n=397)

36 Months of imatinib	198	192	184	152	100	56	13	0
12 Months of imatinib	199	188	176	140	87	46	20	0

Key clinical question

How should patients be treated in the adjuvant setting when the resected tumour has primarily an exon 9 mutation?

Observations

- The principles underlying “personalized medicine” apply equally in GIST.
- However unlike personalized treatment options in other diseases, the treatment options remain the same whatever the personalized approaches dictate.
- Hence it’s possible to treat patients with GIST without knowledge of mutation status
- Perhaps the only exception relates to the use of a high dose of imatinib in patients carrying a GIST with a mutation in Exon 9

Conclusions

- Where possible, mutation analysis is preferred in managing patients with advanced GIST
- If this is not feasible, then caution should be used in managing patients with metastatic GIST arising from the small bowel (or principally peritoneal metastases) as these patients may benefit from early dose escalation or early use of sunitinib
- The absolute role of understanding mutation status for the majority of patients with advanced disease or in the adjuvant setting is still not clear cut.