Gastrointestinal Stromal Tumor

GISTS 2010

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Making Cancer History™

Background

GIST Overview

- Most common GI sarcoma
  - 0.2% of all GI tumors, but 80% of GI sarcomas
- Distinct clinical and histopathologic entity
  - Highest incidence in the 40-60 year age group
  - Similar male/female incidence
  - Many misclassified
- About 5,000 newly diagnosed GIST patients per year in the US
- Clinical presentation is variable
  - pain, hemorrhage, anemia, anorexia, nausea, perforation

Median Overall Survival in Metastatic GIST

Circa 1990

Blanke et al. Abstract 7. GI Cancers Symposium, 2006

Chemotherapy Trials

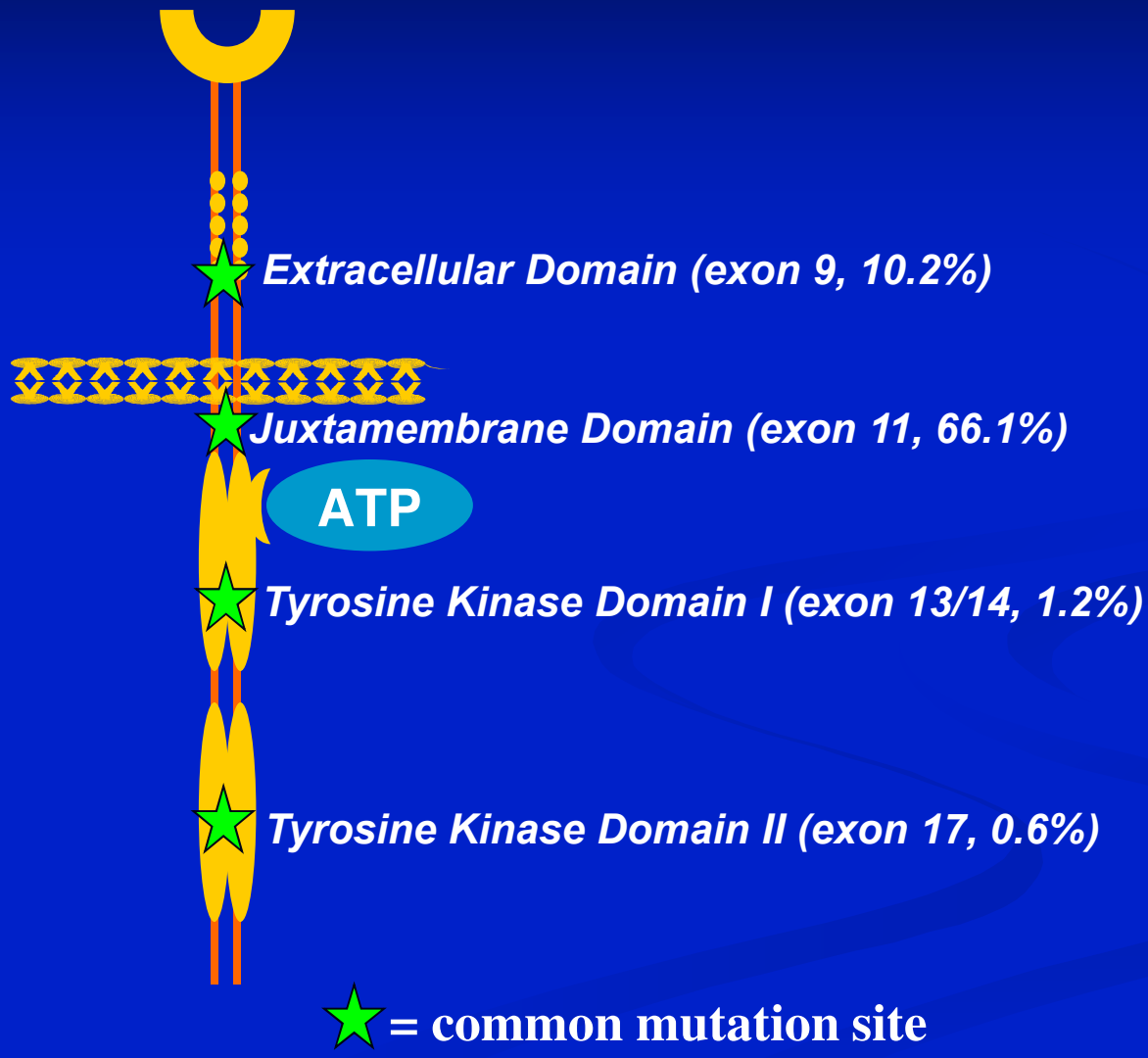
Advanced GIST

Regimen	Number of Patients	Partial Response n (%)
DOX + DTIC	43	3 (7%)
DOX + DTIC +/– IF	60	10 (15%)
IF + VP-16	10	0 (0%)
Paclitaxel	15	1 (7%)
Gemcitabine	17	0 (0%)
Liposomal DOX	15	0 (0%)
DOX	12	0 (0%)
DOX or docetaxel	9	0 (0%)
High-dose IF	26	0 (0%)
EPI + IF	13	0 (0%)
Various	40	4 (10%)
DTIC/MMC/DOX/ CDDP/GM–CSF	21	1 (5%)
Temozolamide	19	0 (0%)
TOTAL	**280**	**19 (6.8%)**

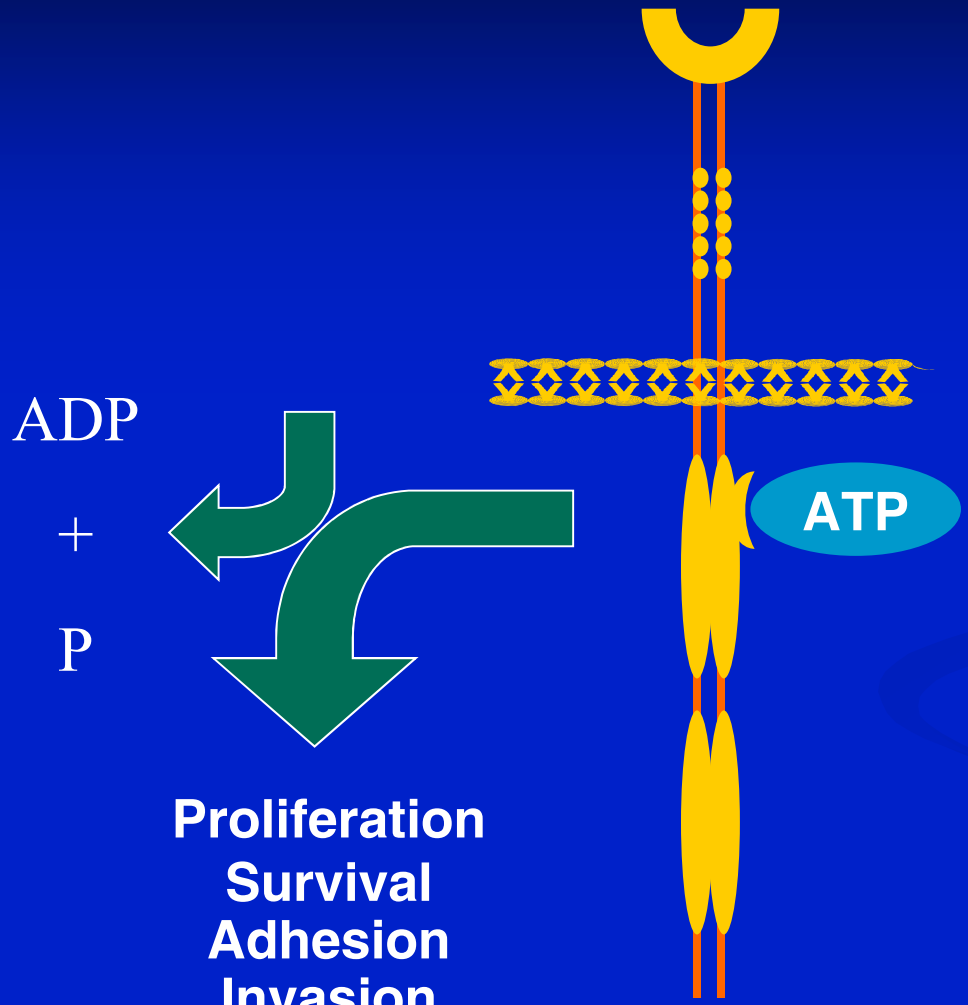
GIST Pathology

- GIST share several characteristics with ICC
  - Neuromuscular pacemaker cell of the GI tract
  - Found in myenteric plexus throughout GI tract
  - Expression of CD34 in ~80% of cases
  - Expression of KIT (CD117) in ~95% of cases

Kit Receptor Structure

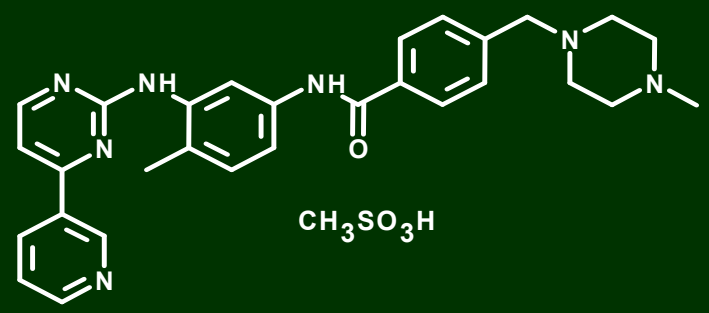


Kit Receptor Phenotype



Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

Imatinib Mesylate



Formula: $C_{30}H_{35}N_7SO_4$

MW: 589.7

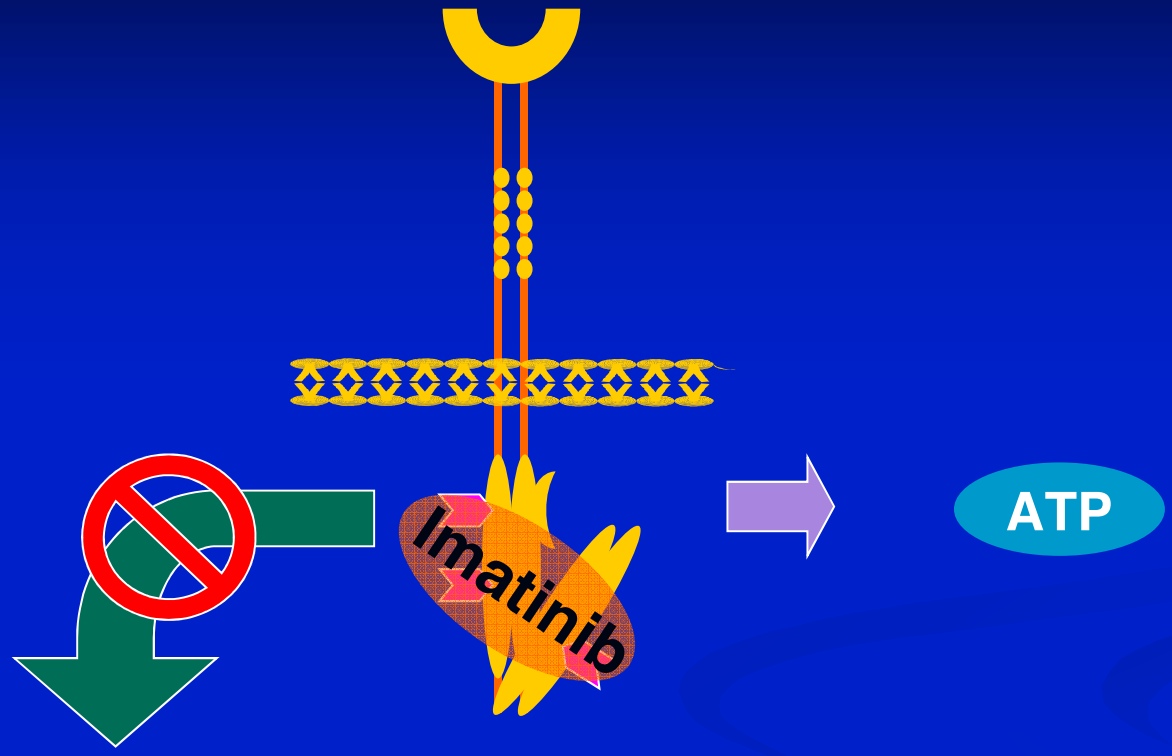
- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

Inhibitor of selective tyrosine kinases

bcr-abl
PDGF-R
c-kit

} Potent ($IC_{50} \approx 0.1\mu M$)

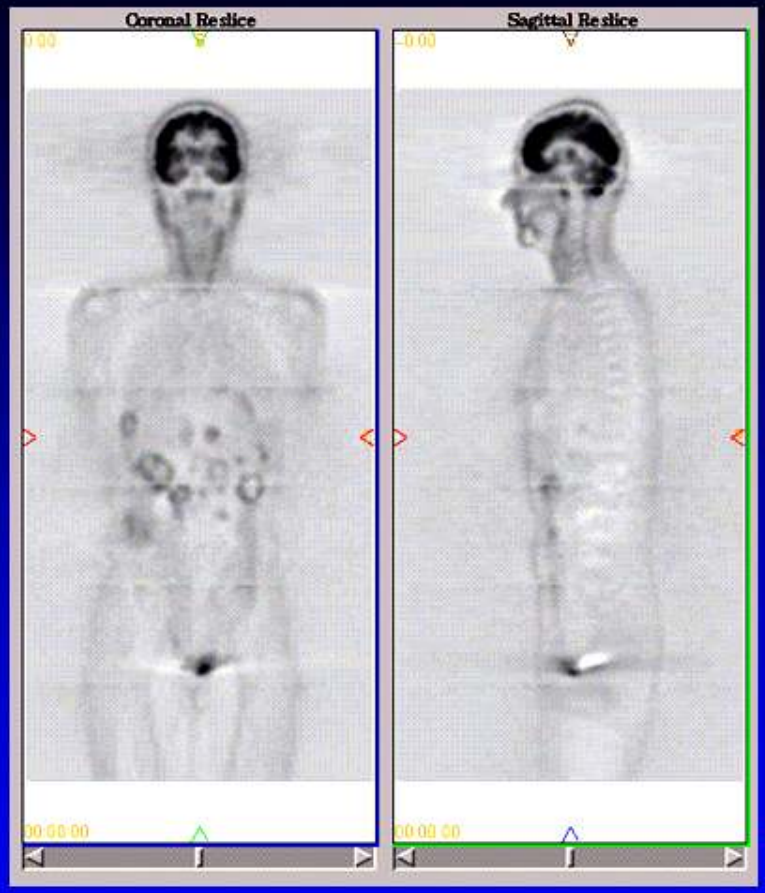
Kit Receptor Phenotype



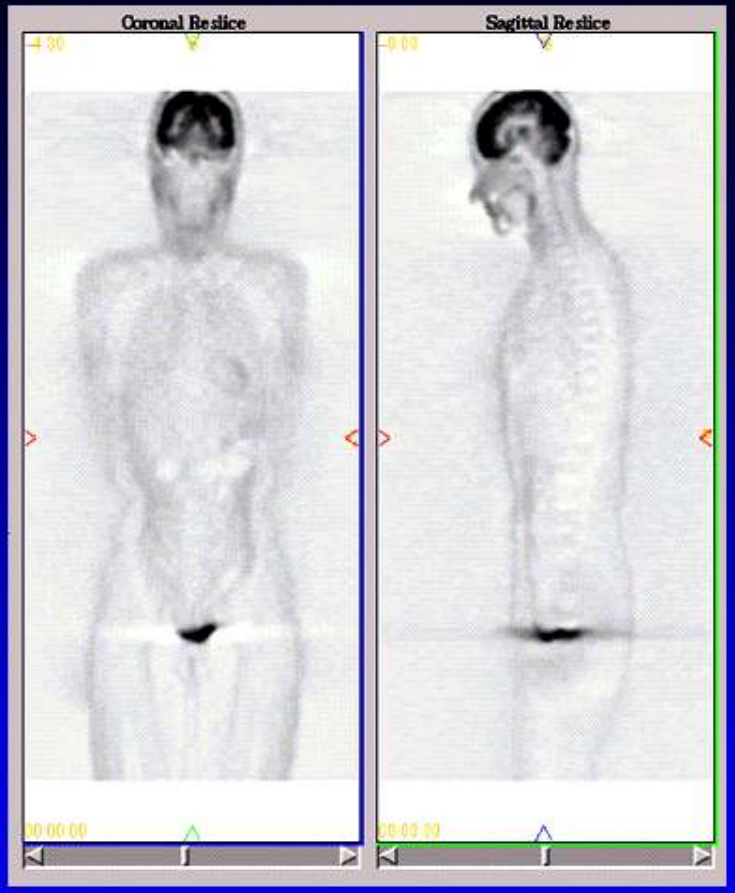
Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= imanitib contact point

Marked Biologic Response Revealed by PET Scan



Multiple liver and upper abdominal ^{18}FDG-accumulating metastases



A marked decrease in ^{18}FDG uptake 4 weeks after starting imatinib mesylate

Joensuu H et al *N Engl J Med* 2001;344:1052-1056.

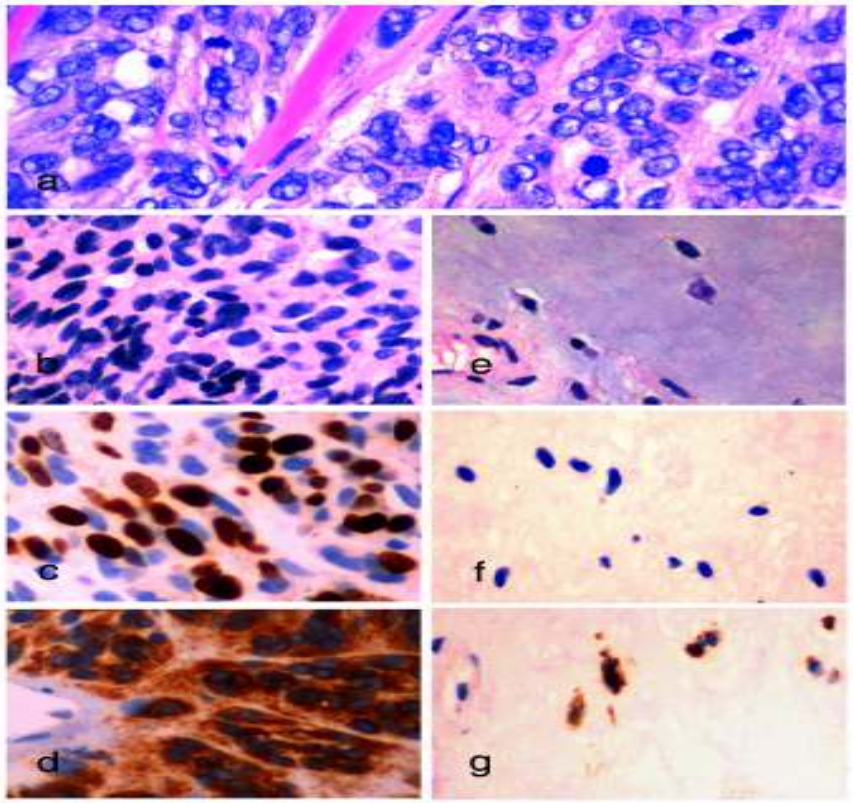
The First GIST Patient: Histology

***H&E** (at diagnosis)*

H&E

Ki 67

CD117



Pretreatment

One month of therapy

Joensuu H et al. *N Engl J Med*. 2001;344:1052-1056.

What is the chance of imatinib helping me?

Clinical Trials of Imatinib in GIST

Study	Phase	N	OR	CR	PR	SD	PD	OS (2 yr)	TTP (median)	PFS
van Oosterom, 2001	I	36	53%	0%	53%	36%	11%	-	-	-
von Mehren, 2002	II	147	63%	0%	63%	19%	12%	-	72 wks	-
Verweij, 2003	II	27	71%	4%	67%	18%	11%	-	-	73% (1 yr)
Rankin, 2004	III	746								
-400 mg daily			48%	3%	45%	-	-	78%	-	50% (2 yr)
-800 mg daily			48%	3%	45%	-	-	73%	-	53% (2 yr)
Verweij, 2004	III	946								
-400 mg daily			50%	5%	45%	32%	13%	69%	-	44% (2 yr)
-800 mg daily			54%	6%	48%	32%	9%	74%	-	52% (2 yr)

Courtesy Dejka Steinert, M.D.

Phase III dose-randomized study of Imatinib mesylate (Gleevec, STI571) for GIST: NA Intergroup S0033 early results.

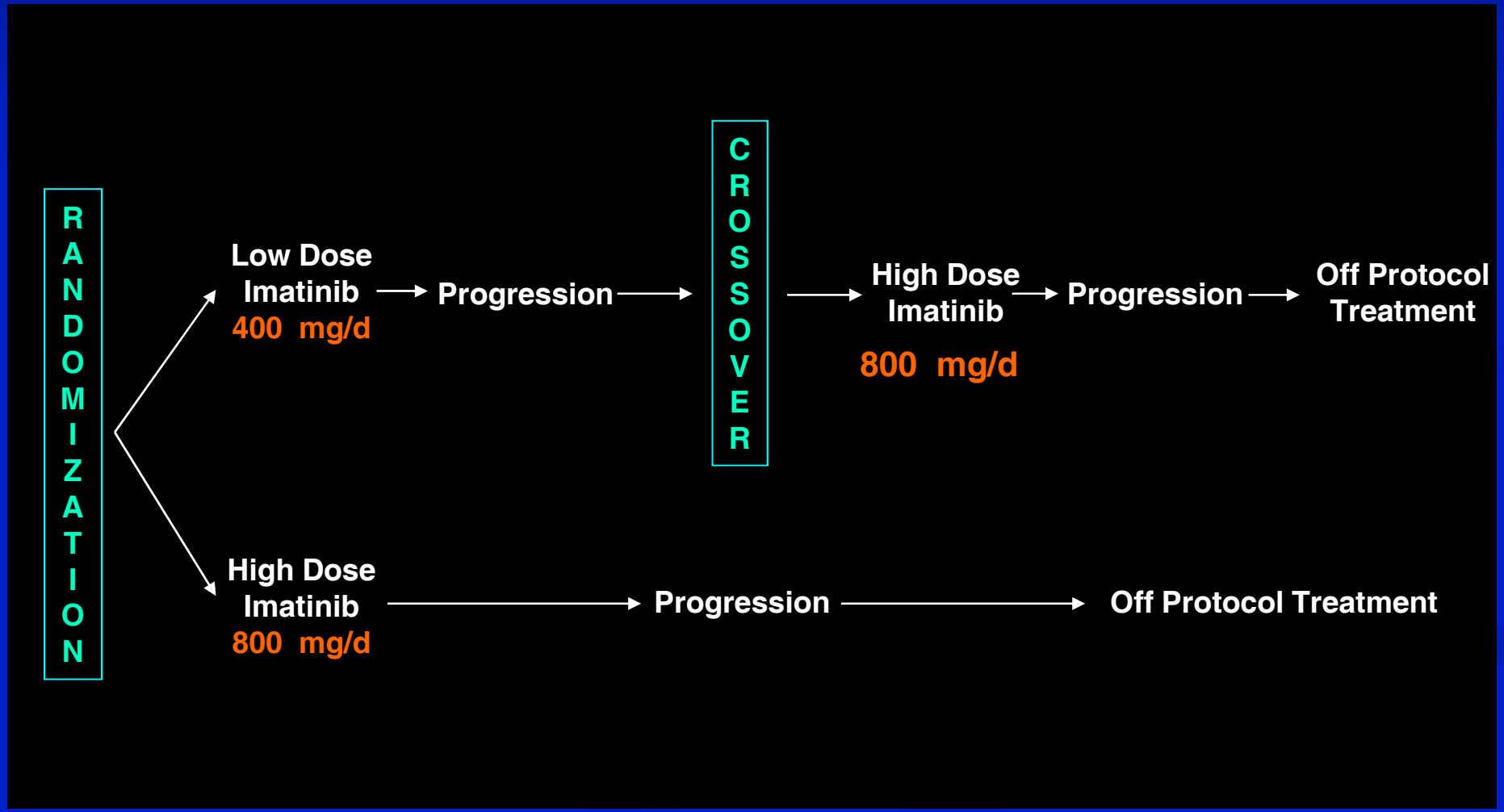
Robert S. Benjamin, UT MD Anderson Cancer Center and SWOG, Houston, TX, Cathryn Rankin, SWOG, Christopher Fletcher, Dana Farber Cancer Institute, Charles Blanke, SWOG, Margaret von Mehren, ECOG, Robert Maki, CALGB, Vivien Bramwell, NCIC, Laurence Baker, SWOG, Ernest Borden, SWOG, George D. Demetri, Dana Farber Cancer Institute, CALGB, as the

North American Sarcoma Intergroup

Benjamin et al, ASCO 2003

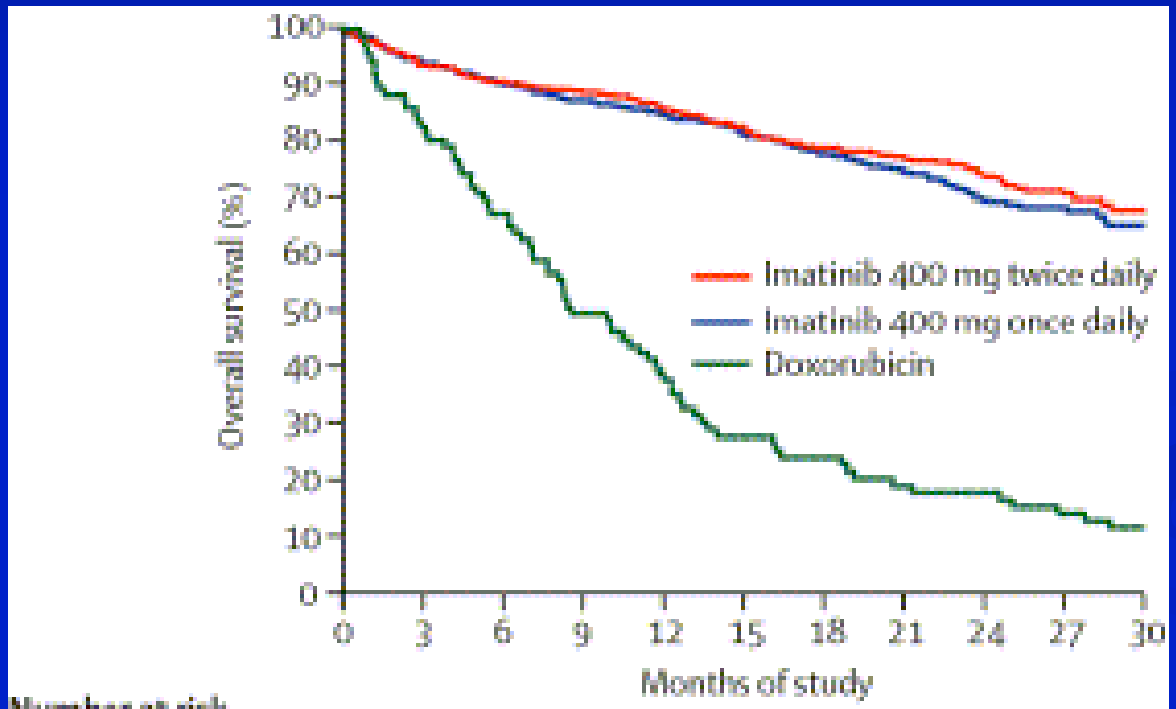
North American Sarcoma Intergroup

Schema



EORTC Phase III Imatinib for Advanced GIST

Survival Benefit



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

Verweij, et al 2004

How long do I take imatinib?

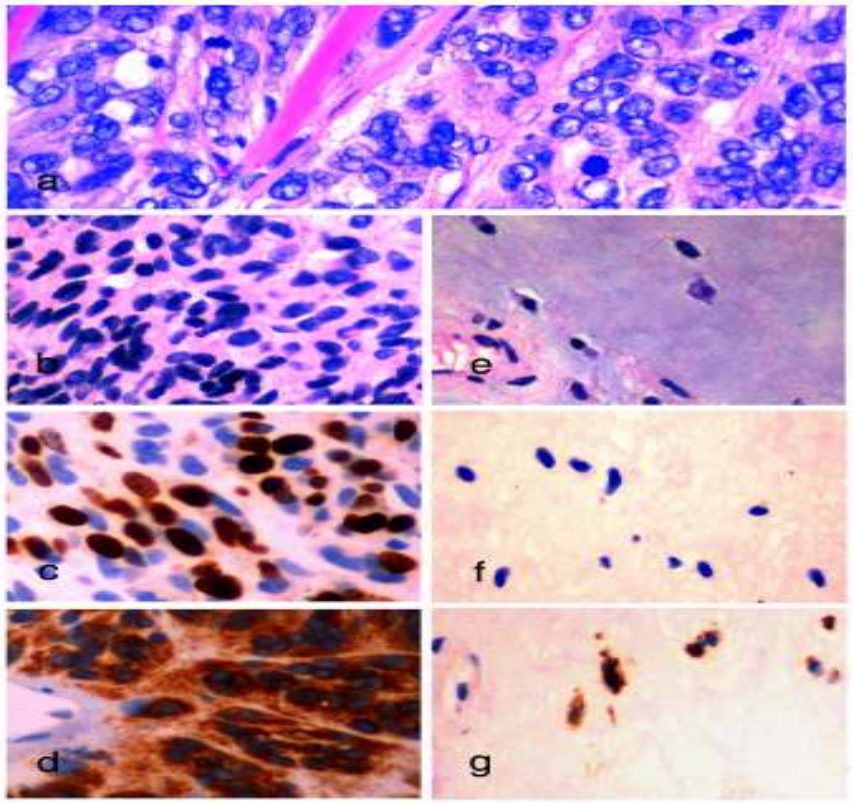
The First GIST Patient: Histology

***H&E** (at diagnosis)*

H&E

Ki 67

CD117

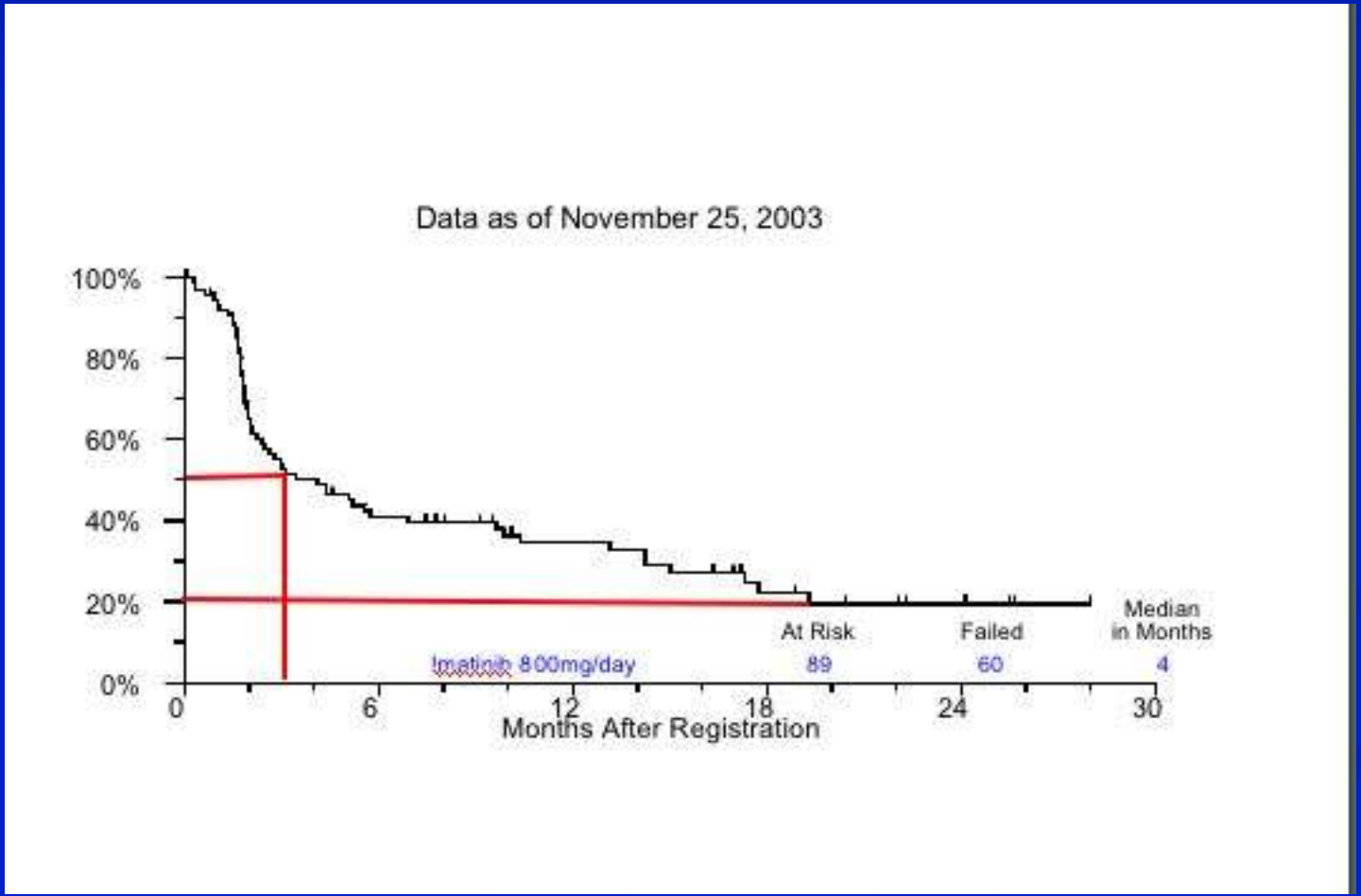


Pretreatment

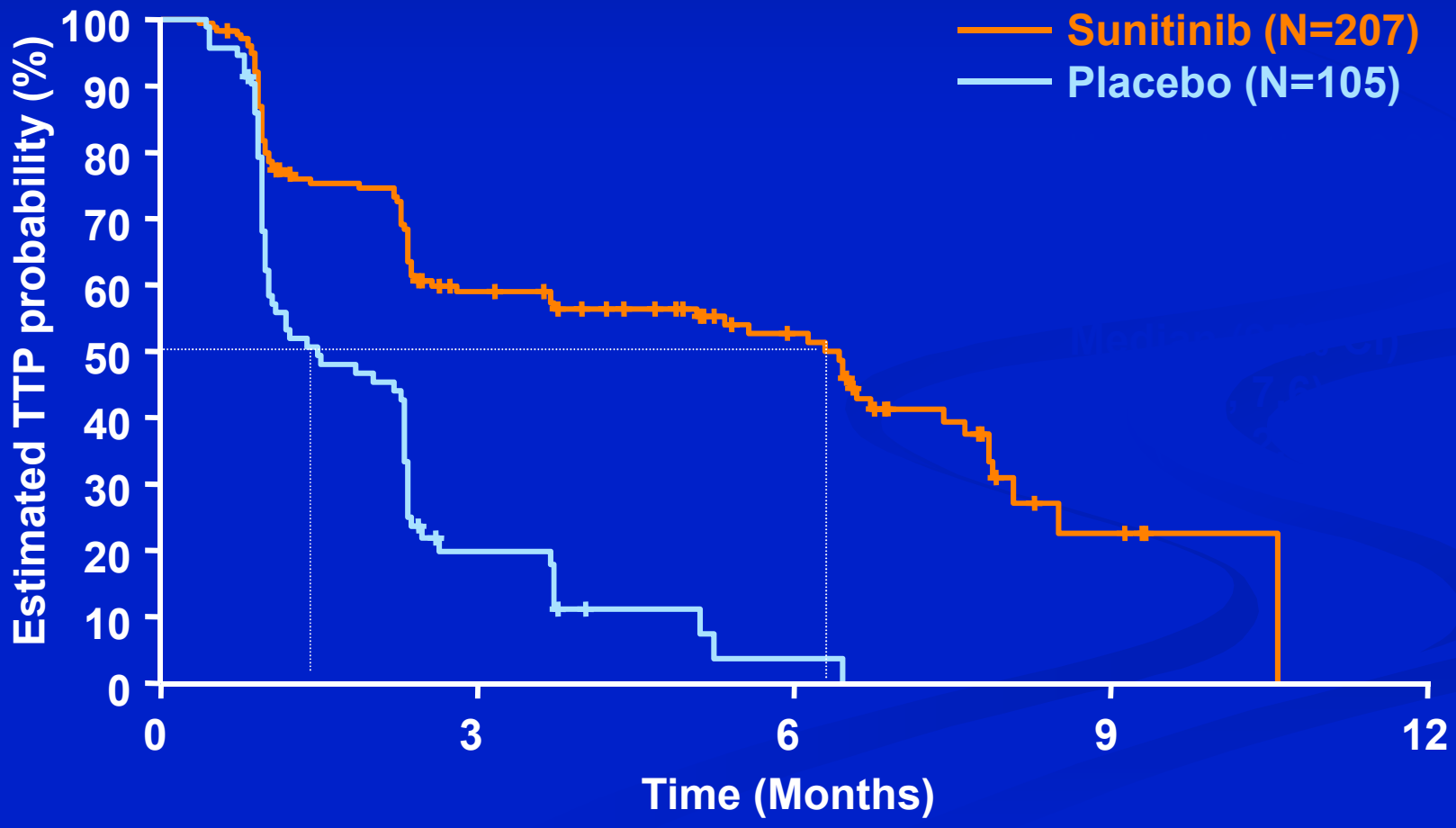
One month of therapy

Joensuu H et al. *N Engl J Med*. 2001;344:1052-1056.

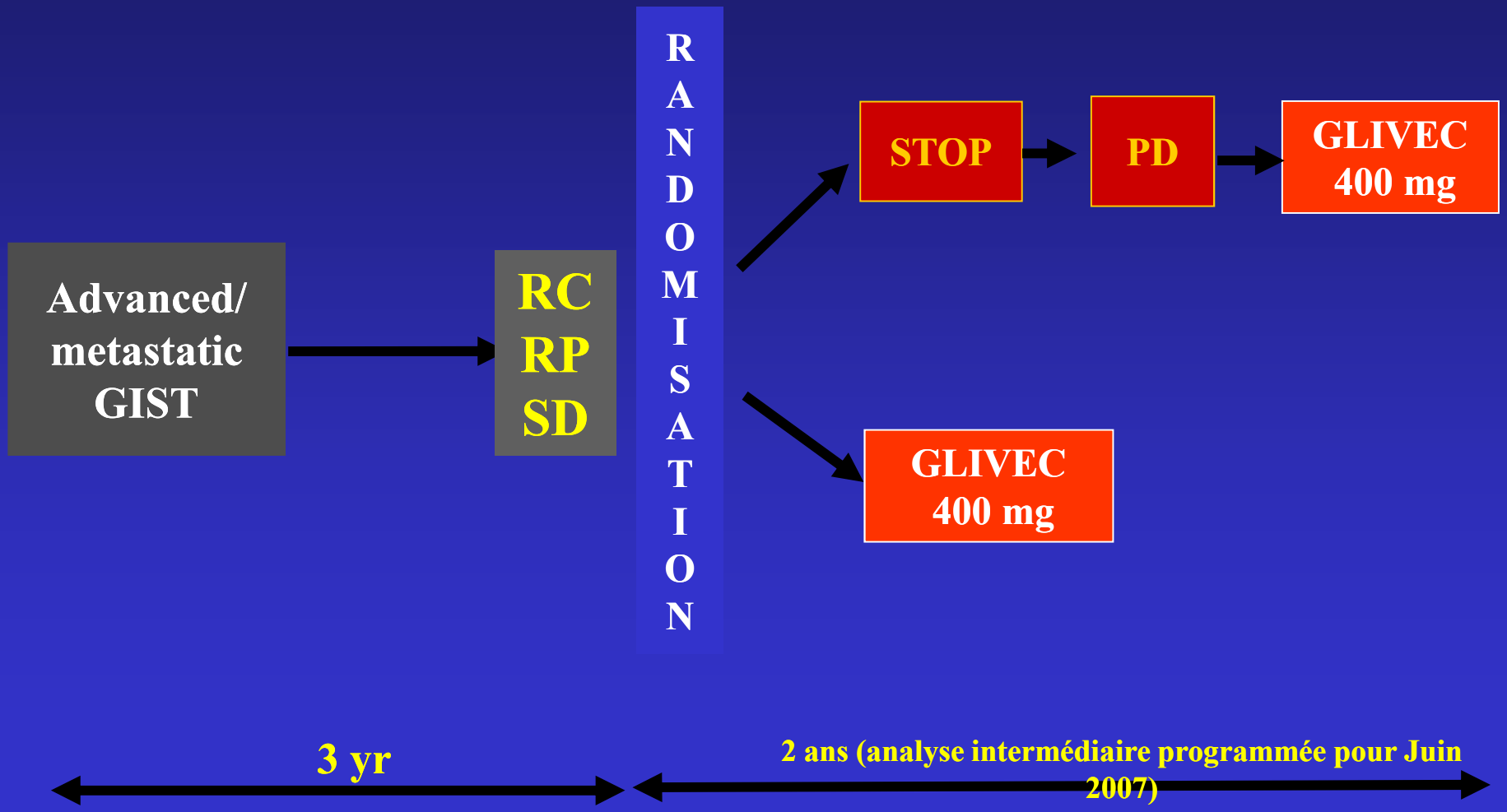
Phase III Trial: US Intergroup S0033: Time to Progression on Crossover



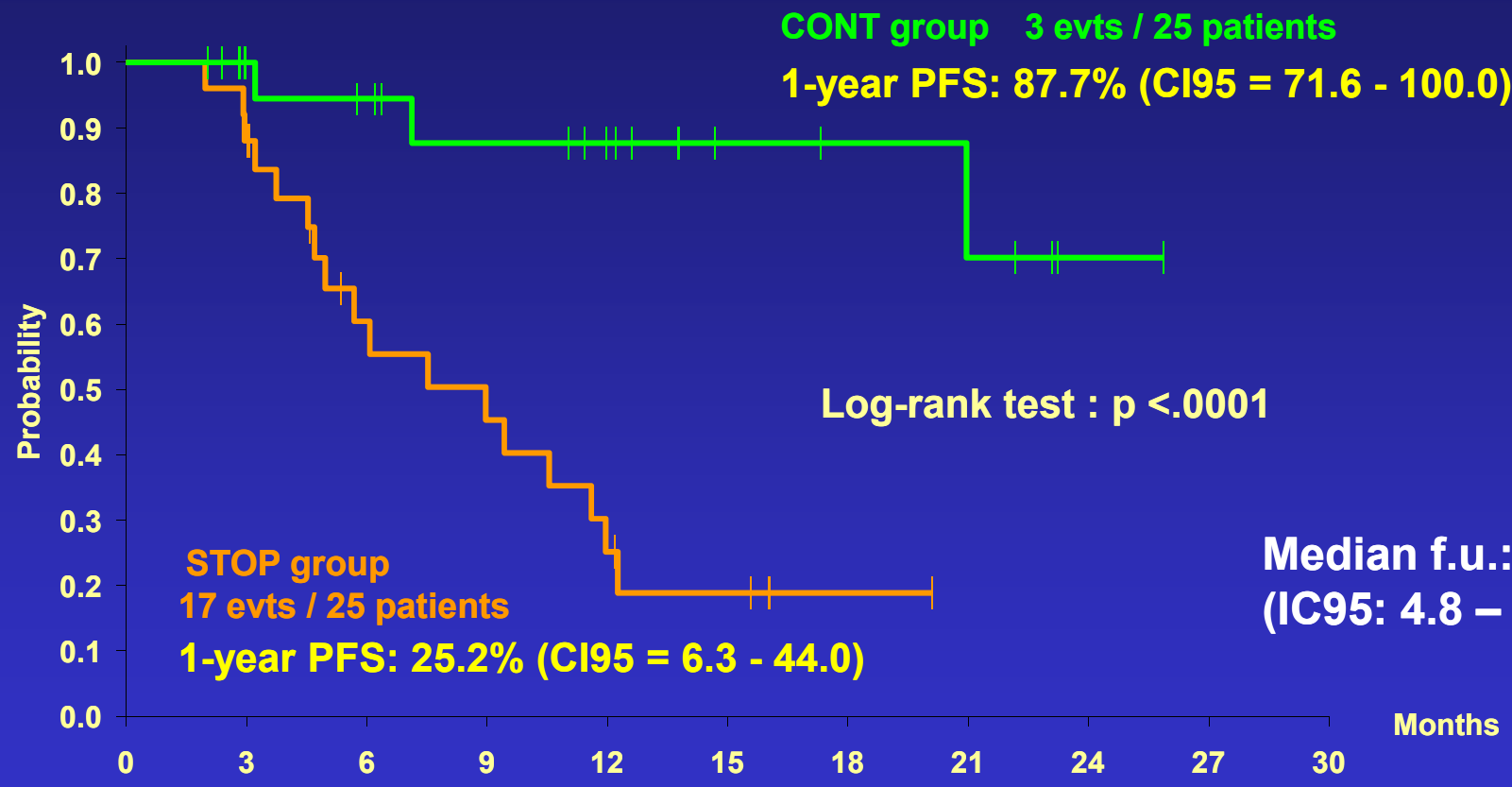
Time to Tumor Progression



BFR14 3-yr randomization



BFR14 3-yr randomization
Progression Free Survival



Rate of PD in STOP group

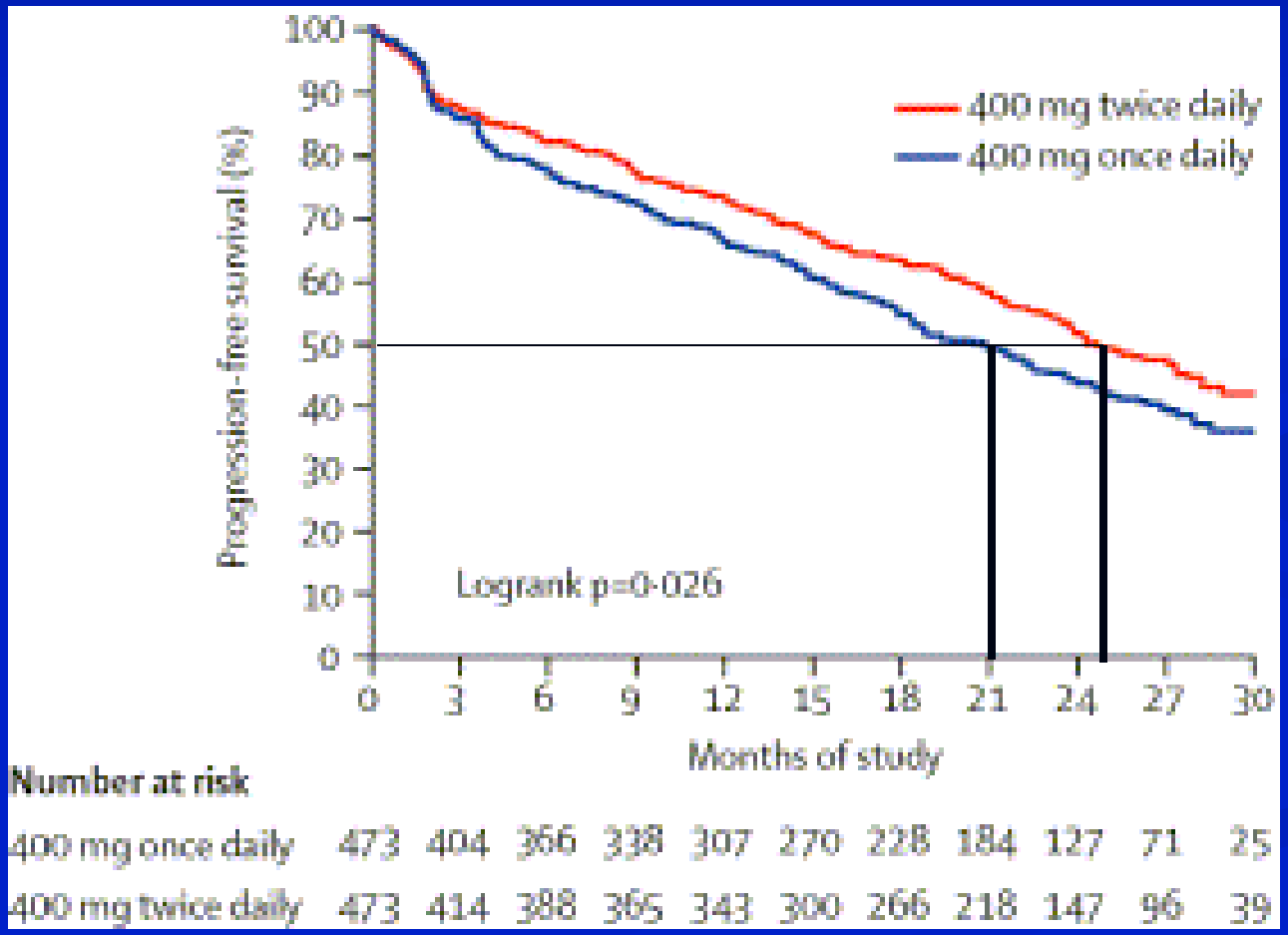
at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Updated sept 07, ECCO 14

What dose of imatinib should I take?

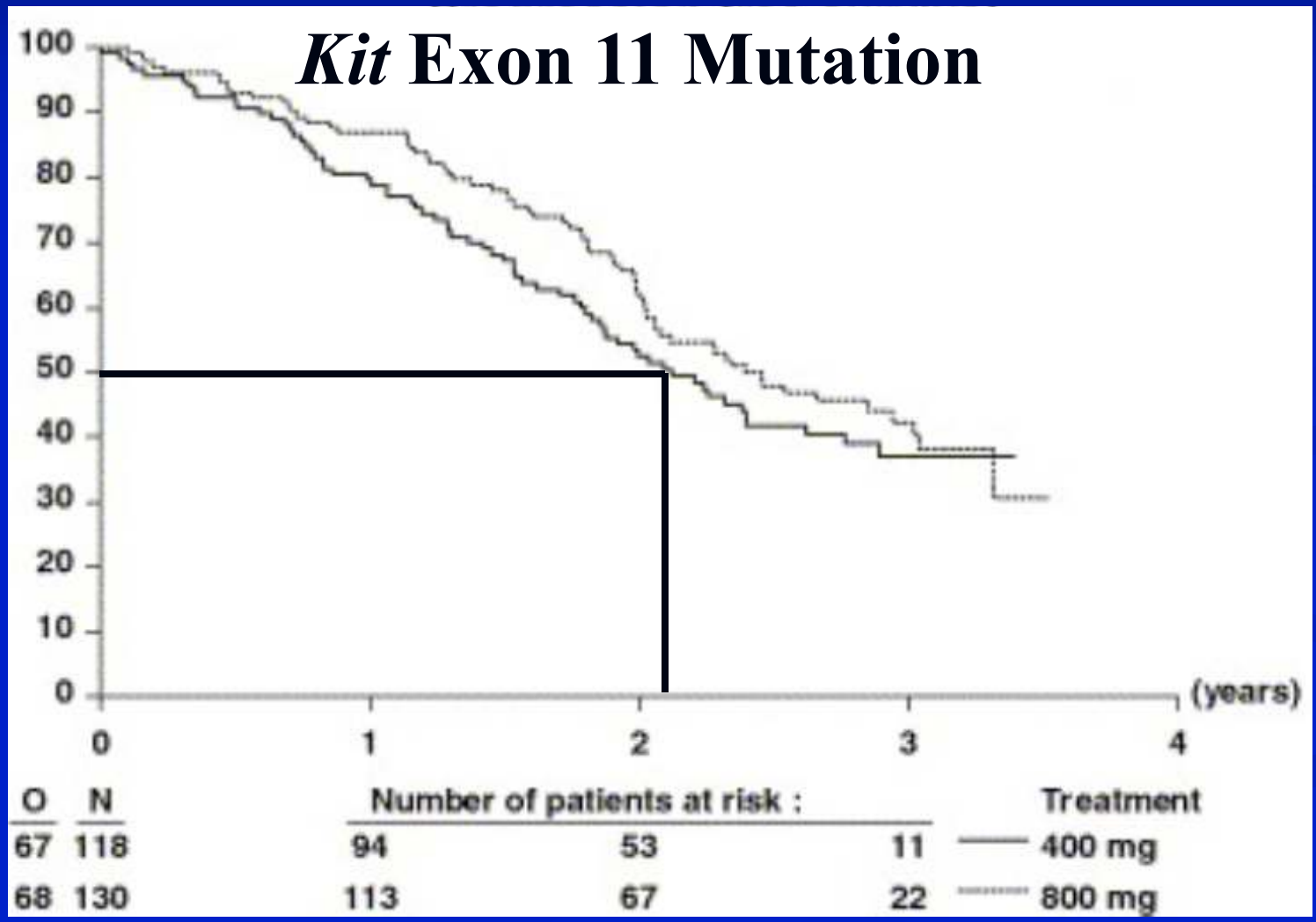
EORTC Phase III Imatinib for Advanced GIST

Progression-free Survival Benefit



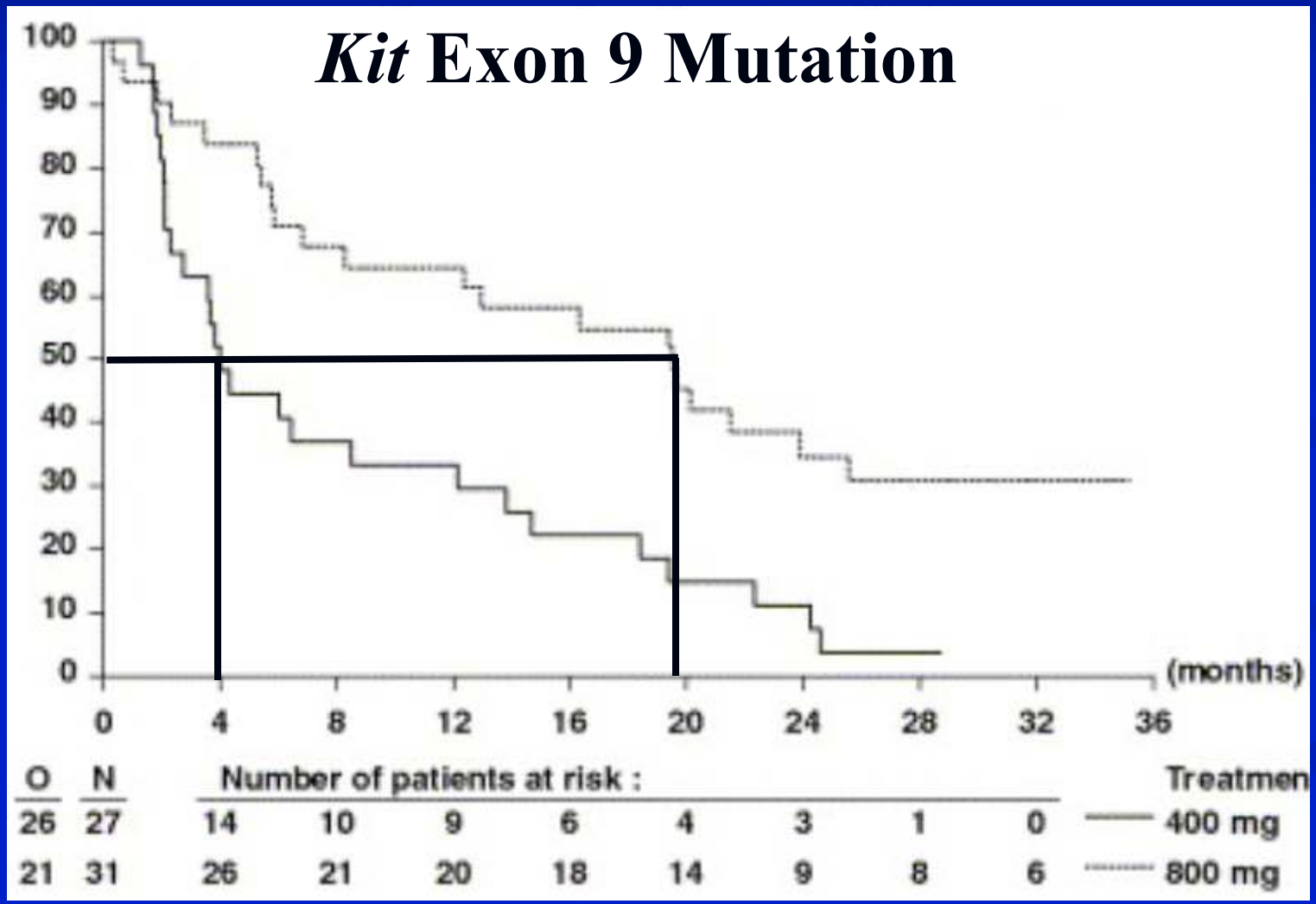
Verweij, et al 2004

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 2007

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 2007

Kit Mutation in GIST

Benefit from 800mg Imatinib

	Odds Ratio	P-value
Exon 11 (n=211)	1.0	0.96
Exon 9 (n=25)	8.0	0.03
Wild-type (n=33)	1.5	0.62

Heinrich et al, ASCO 2005

Tell me about the side effects…..

Side effects: 400 vs. 800 mg

Toxic Event	Adjusted *p*-Value
Edema	<0.001
Anemia	<0.001
Rash	<0.001
Fatigue	<0.001
Nausea	<0.001
Hemorrhage	<0.001
Diarrhea	0.0026
Dyspnea	0.036
Pleuritic Pain	0.053

Verweij et al, 2004

Interruptions and Reductions of Therapy

	400 mg	800 mg
Treatment Interruption	40%	64%
-Hematologic	6%	7%
-Non-Heme	23%	43%
Dose Reduction	16%	60%
-Hematologic	2%	4%
-Non-heme	10%	42%

North American Intergroup Phase III Study of Imatinib in Advanced GIST

Dose Reduction	400 mg (376 pts)	800 mg (370 pts)	800 mg X-Over
1	10%	44%	16%
2	7%	26%	5%
3	2%	11%	0%
4	1%	4%	0%

Dileo et al, ASCO 2005

How do I know if imatinib is working?

Confirmed Overall Responses with Gleevec

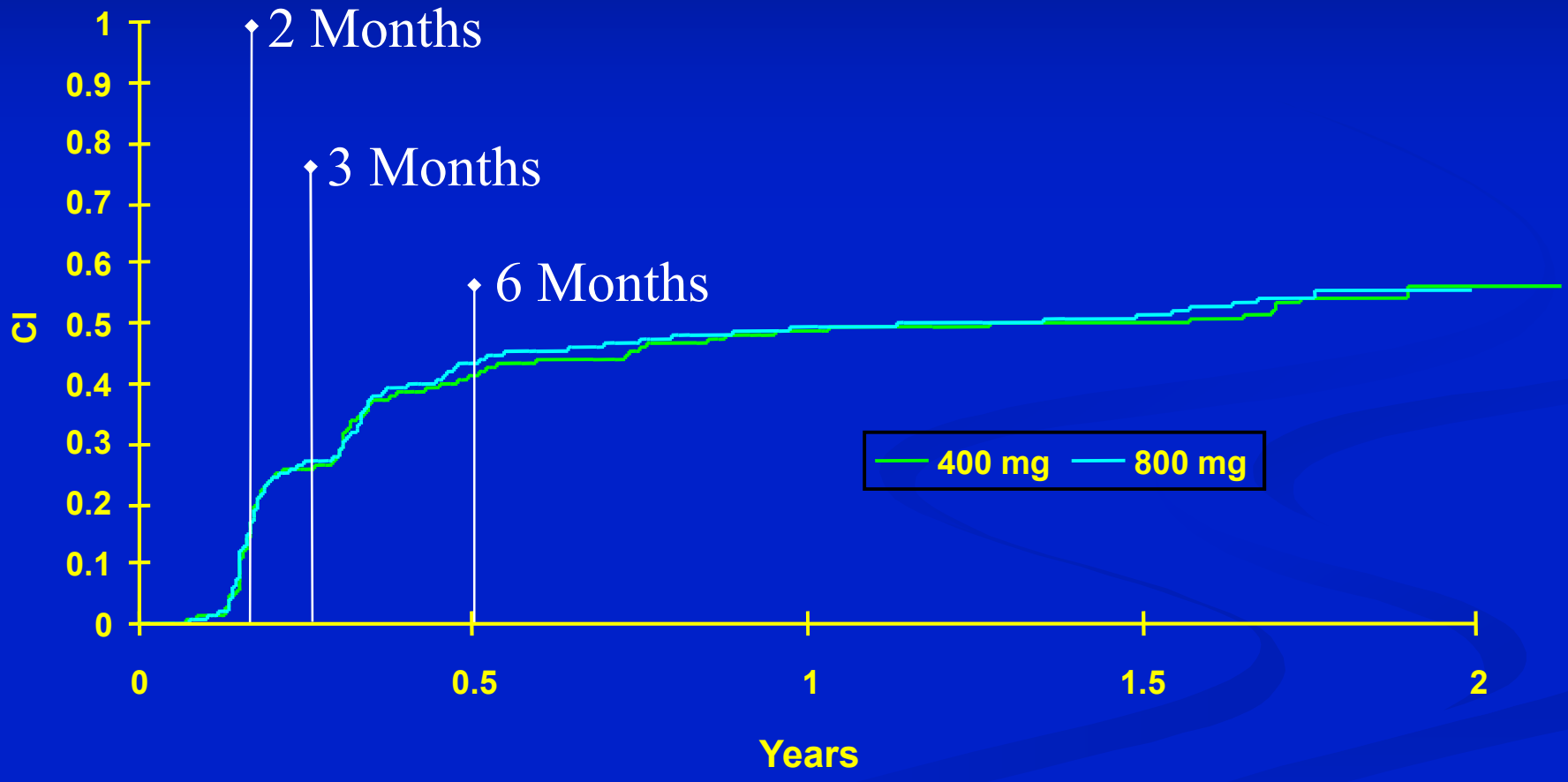
Total patients	N	Confirmed partial response (%)	95% Confidence Interval
400mg	73	33	22-45
600mg	74	43	32-55
Total	147	38	30-46

Best Response (B222)

	400 mg N=73 n (%)	600 mg N=74 n (%)	All Patients N=147 n (%)
Complete Response	0	2 (2.7)	2 (1.4)
Partial Response	50 (68.5)	48(64.9)	98 (66.7)
Stable Disease	10 (13.7)	13 (17.6)	23 (15.6)
Progression	11 (15.1)	6 (8.1)	17 (11.6)
Not evaluable	2 (2.7)	5 (6.8)	7 (4.8)

Time to PR by RECIST

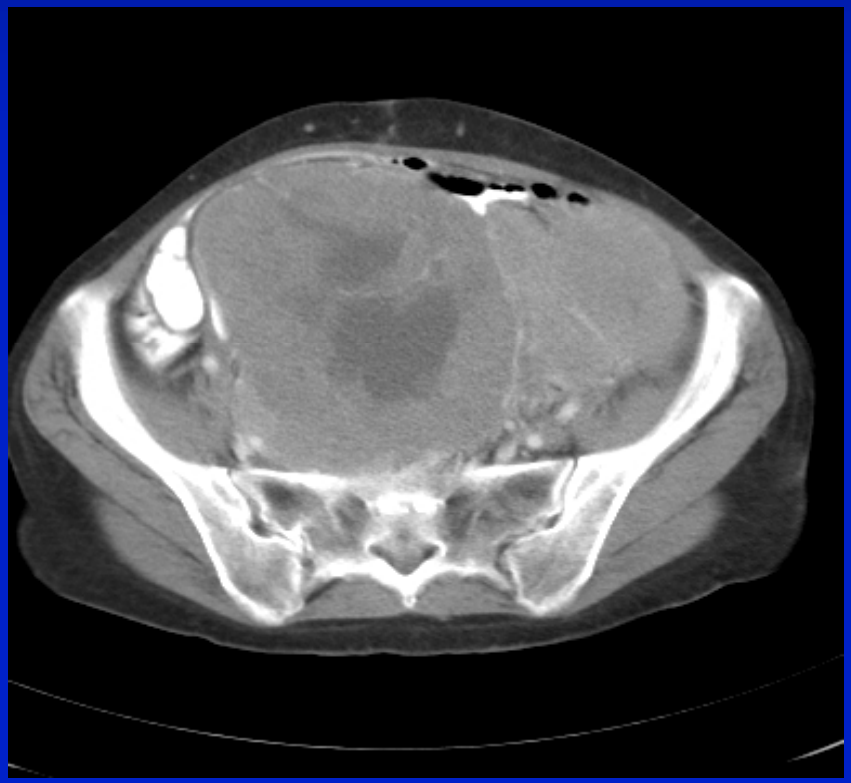
Cumulative incidence of CT responses



Verweij et al, ASCO 2003

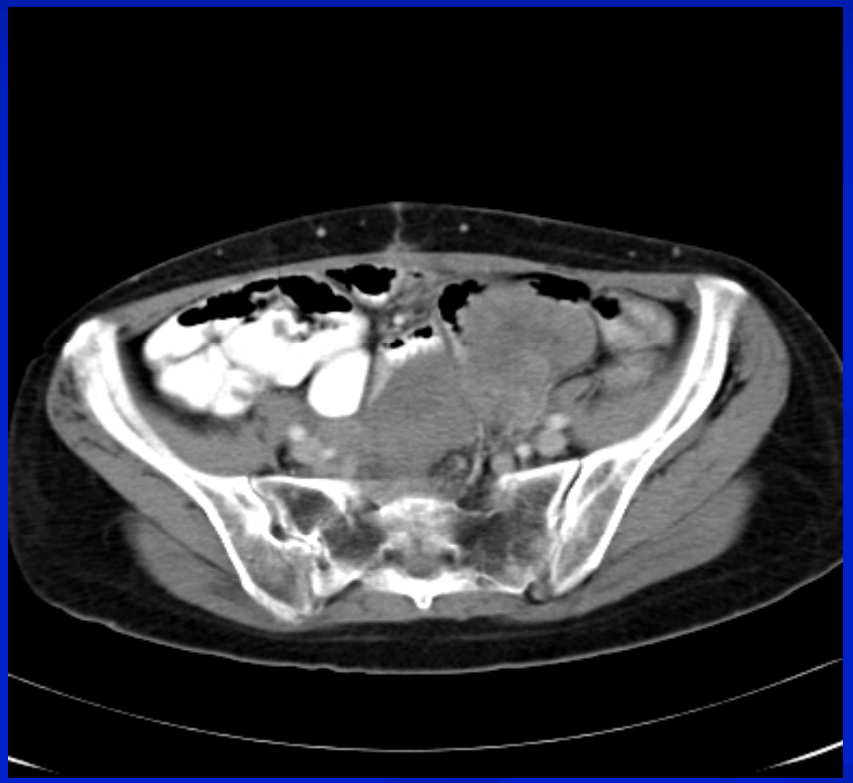
CT Scan Results

Jun 27, 2000



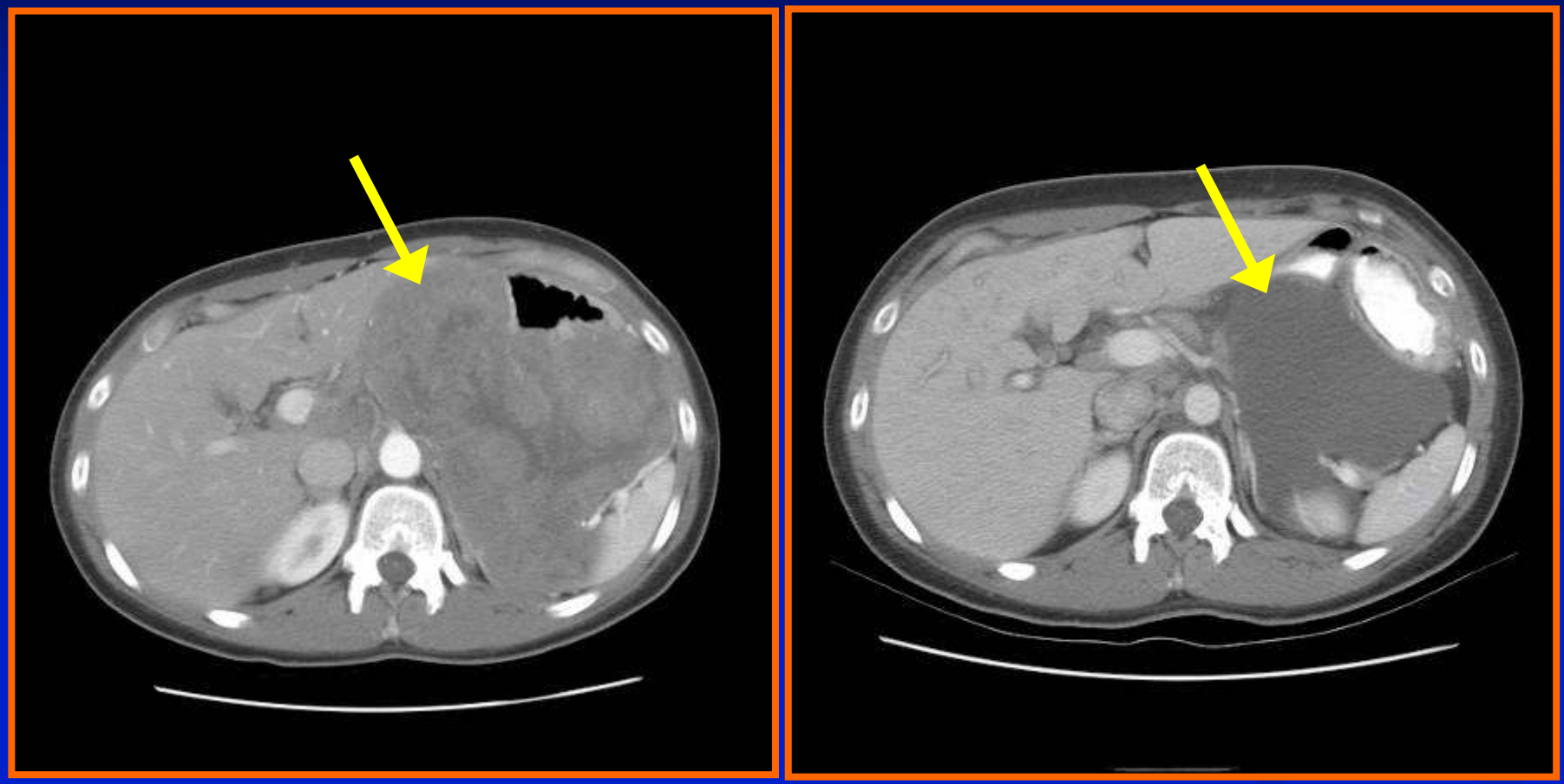
Before Imatinib

Oct 4, 2000



After Imatinib

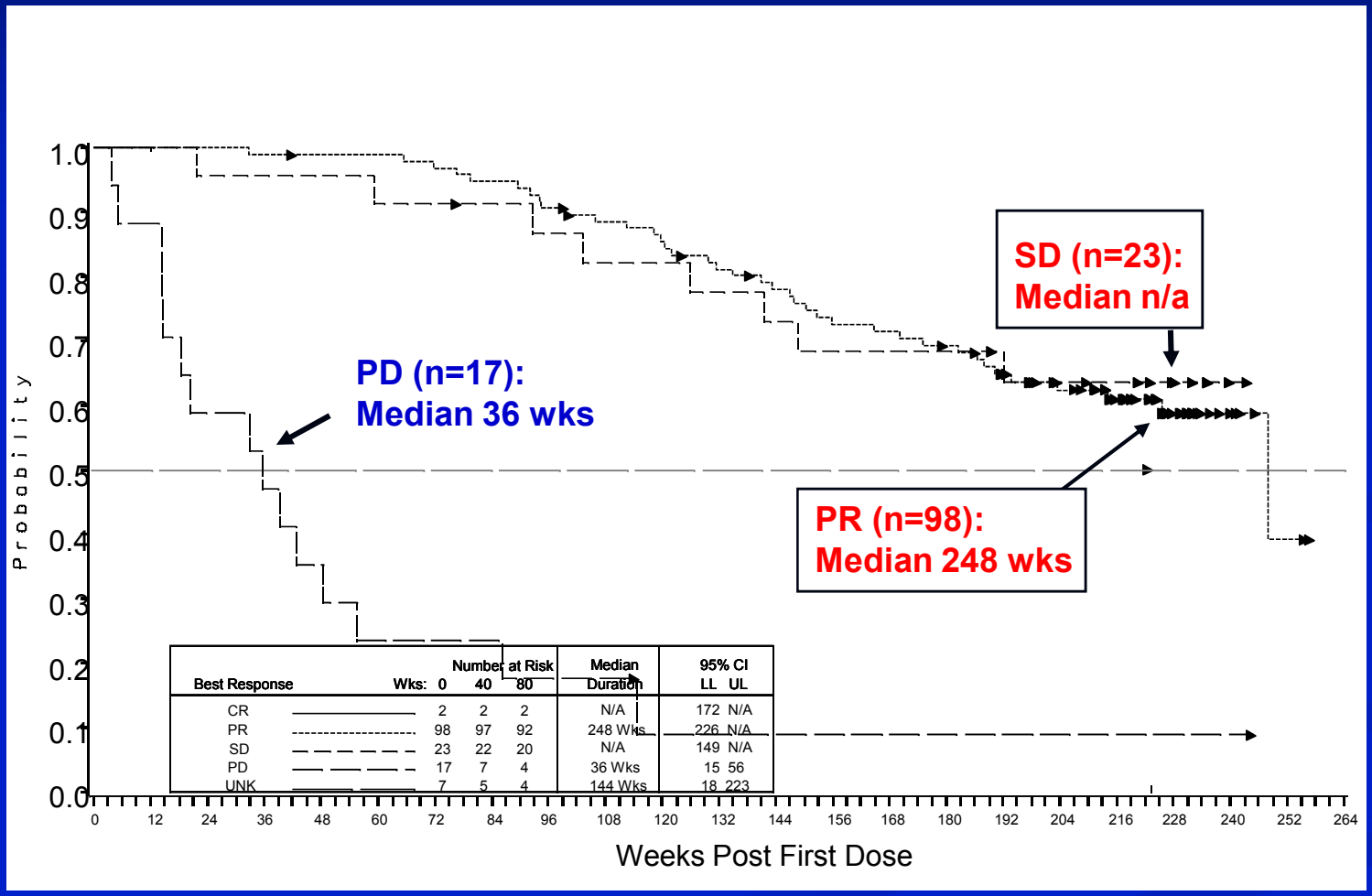
Background (cont)



Decrease in GIST intravenous contrast uptake after patient is treated for 8 weeks with imatinib mesylate

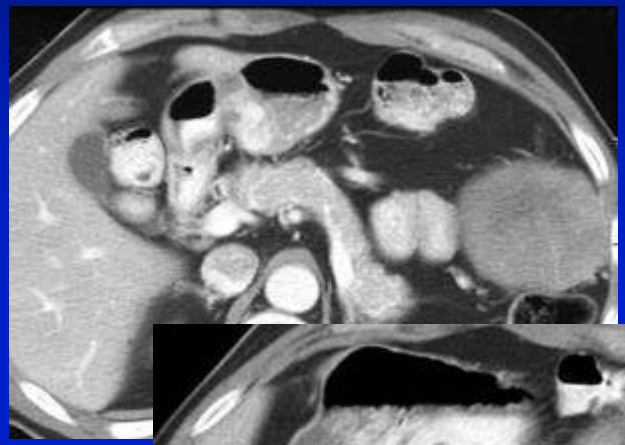
Overall Survival by Best Response

(B222, Kaplan Meier Estimate)

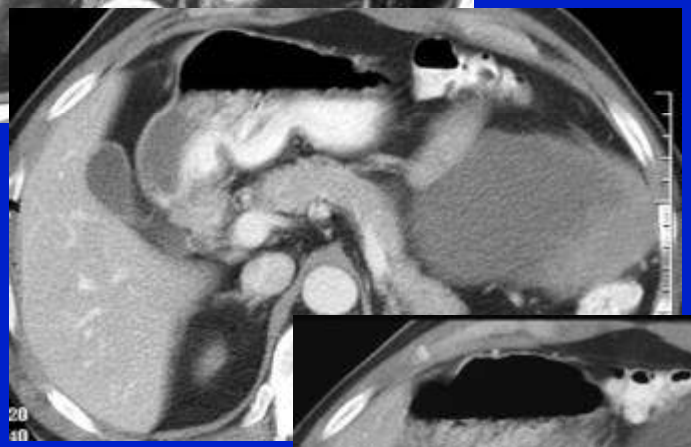


[CR (n=2; median OS n/a) and unknown/NE (n=7; median OS 144 wks) not included]

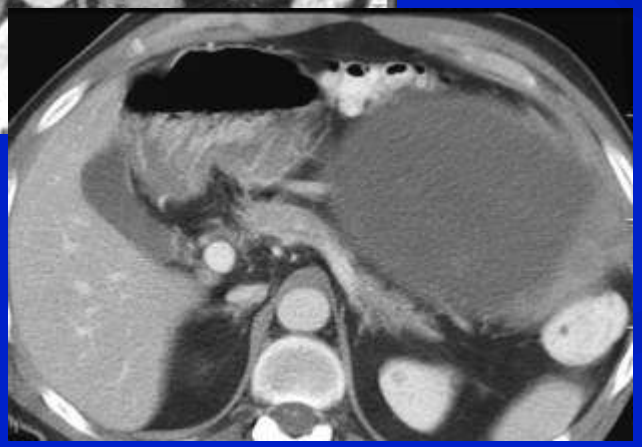
Effects of Imatinib on GIST: CT and PET findings



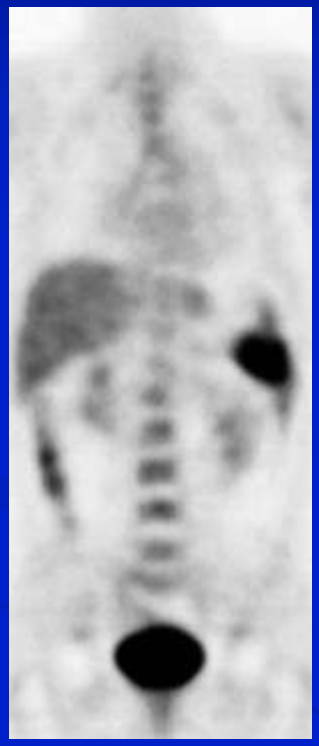
1/18



3/23



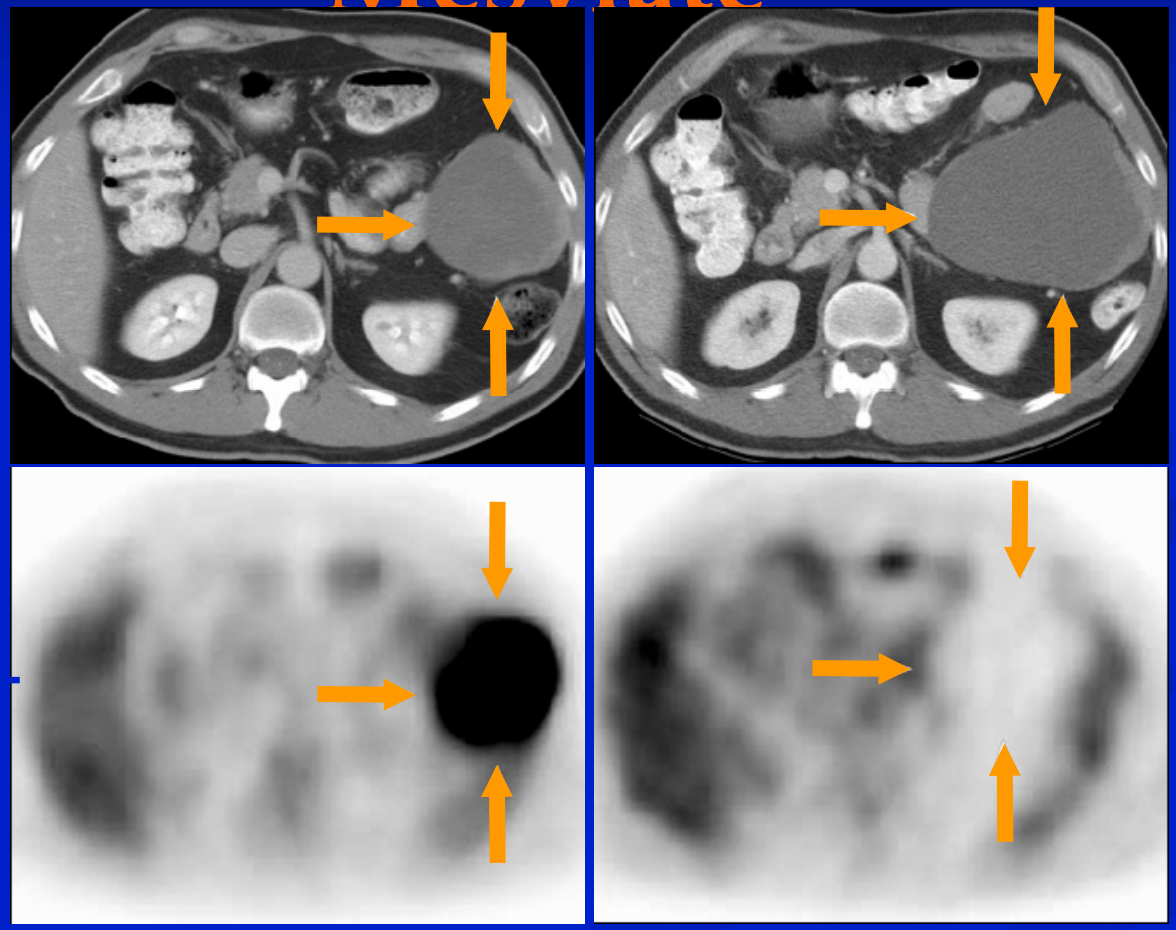
10/8



1/26

3/22

Pseudoprogression Early During Treatment With Imatinib Mesylate



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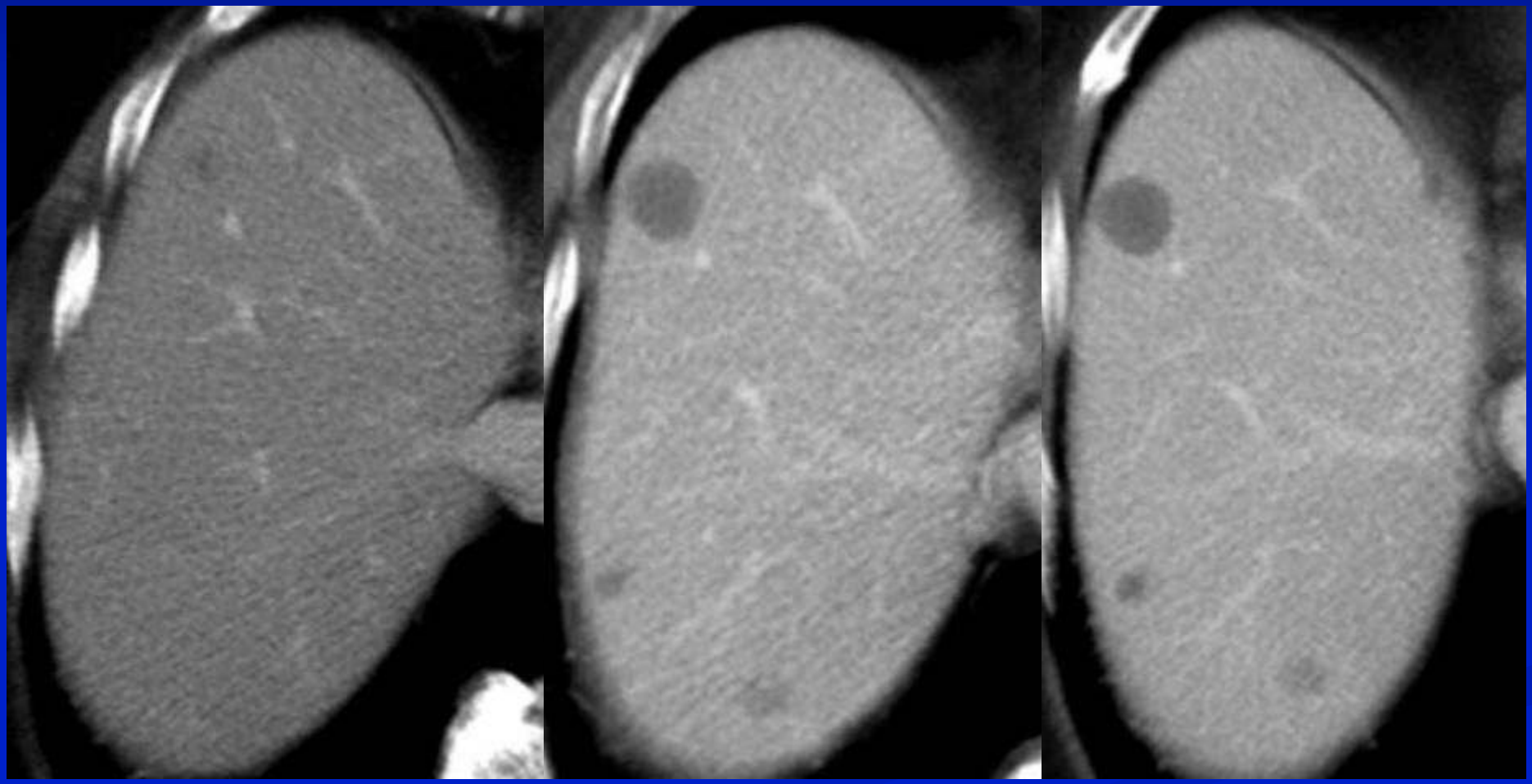
Effects of Imatinib on GIST: CT findings



1/12 3/30 5/24

Modified RECIST for GIST

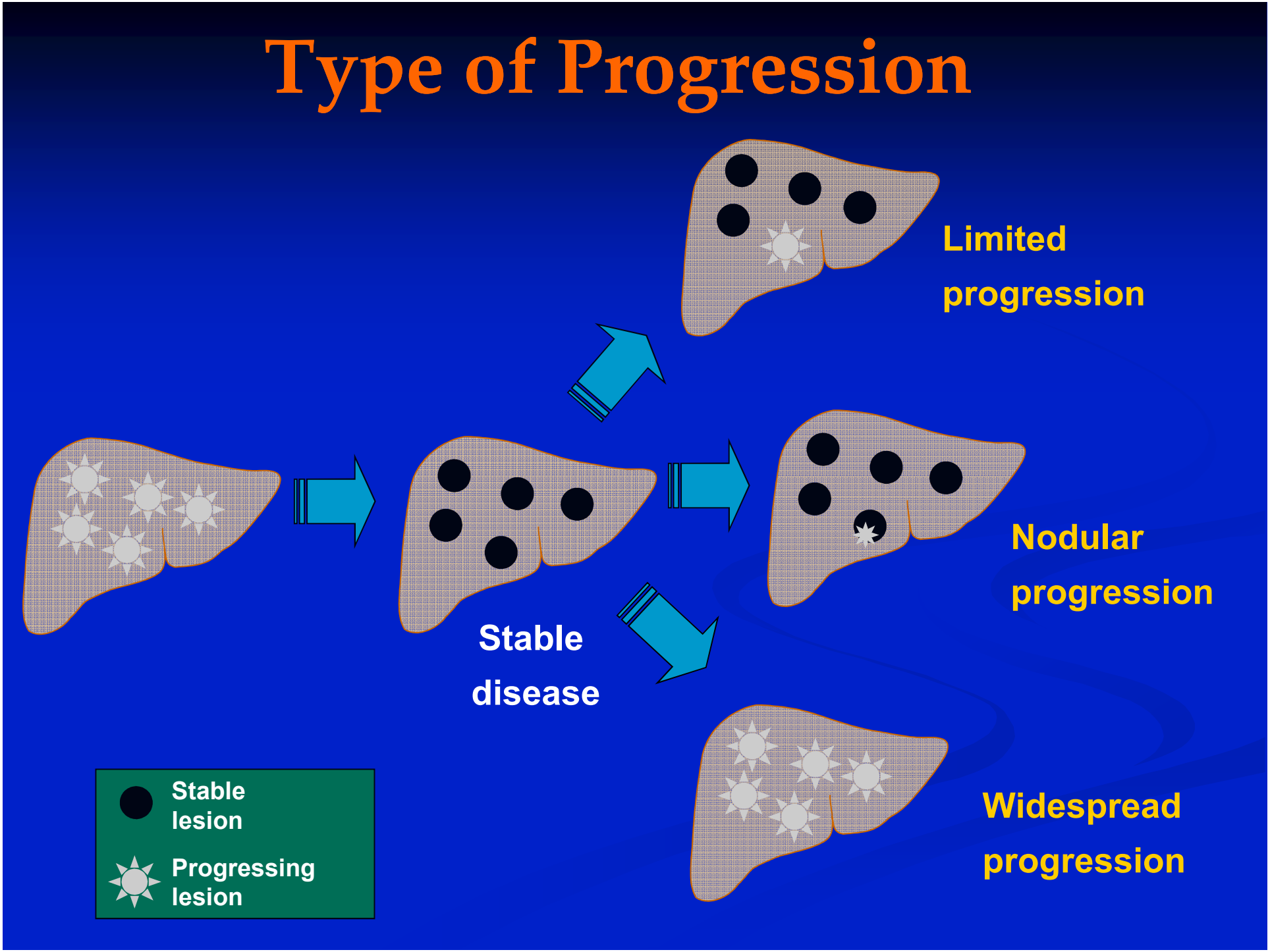
CT Size + Density (Choi)

- Tumor size decrease of ≥10% or tumor density decrease of ≥15% were highly correlated with decrease in SUV by >70% to a value <2.5 on PET.

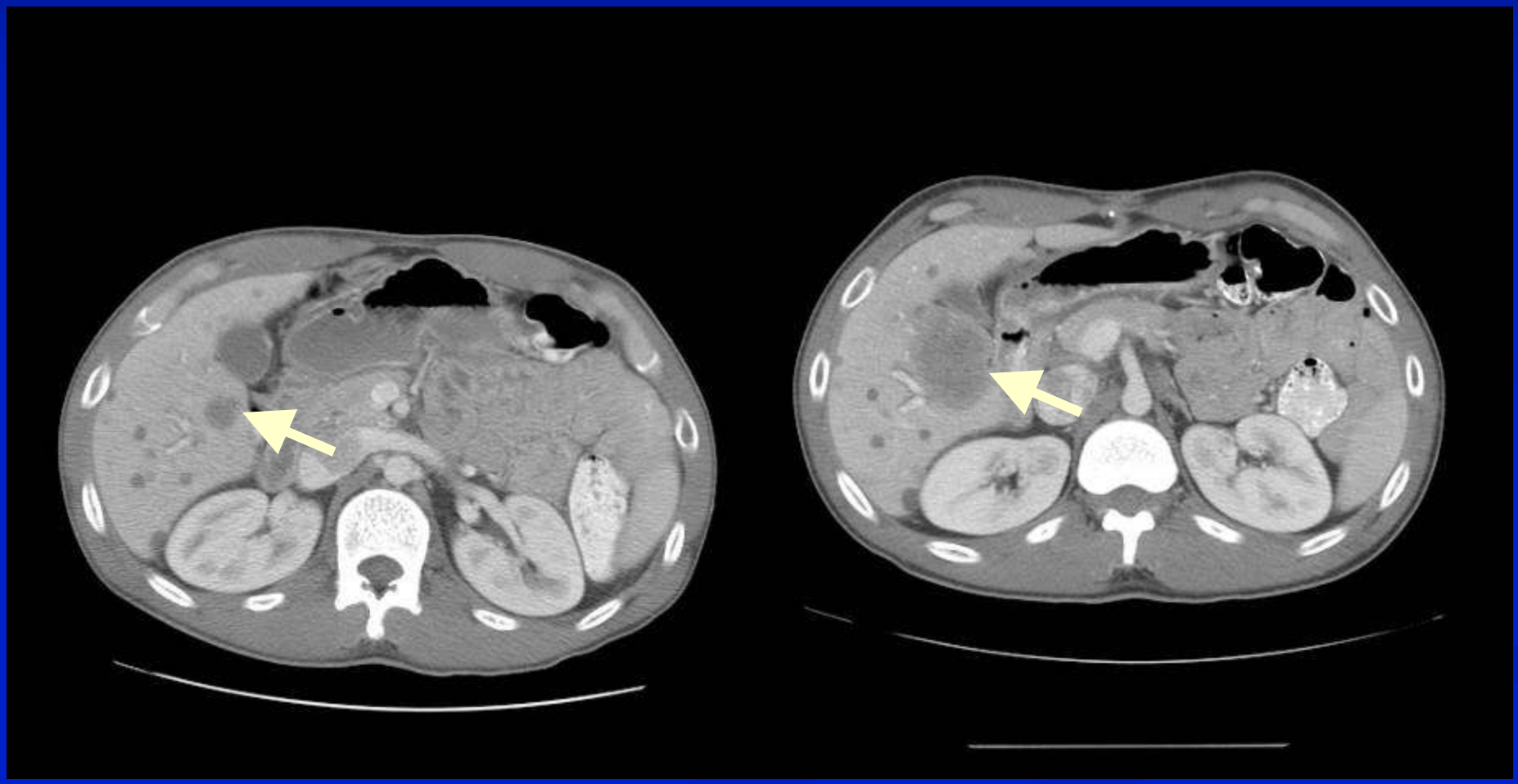
- RECIST criteria substantially underestimate, at least initially, the value of therapy with imatinib for GIST.

How do I know if my GIST comes back?

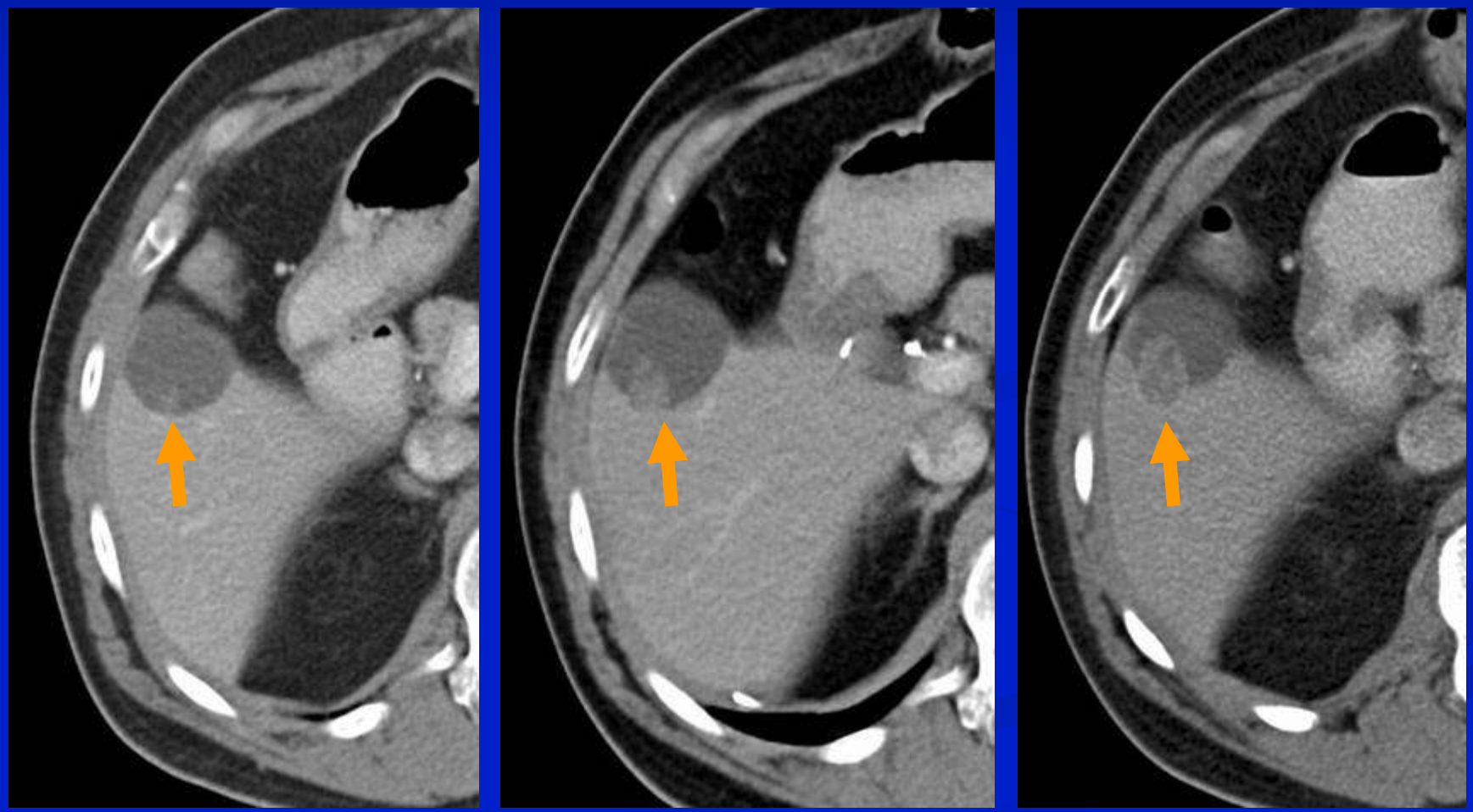
Type of Progression



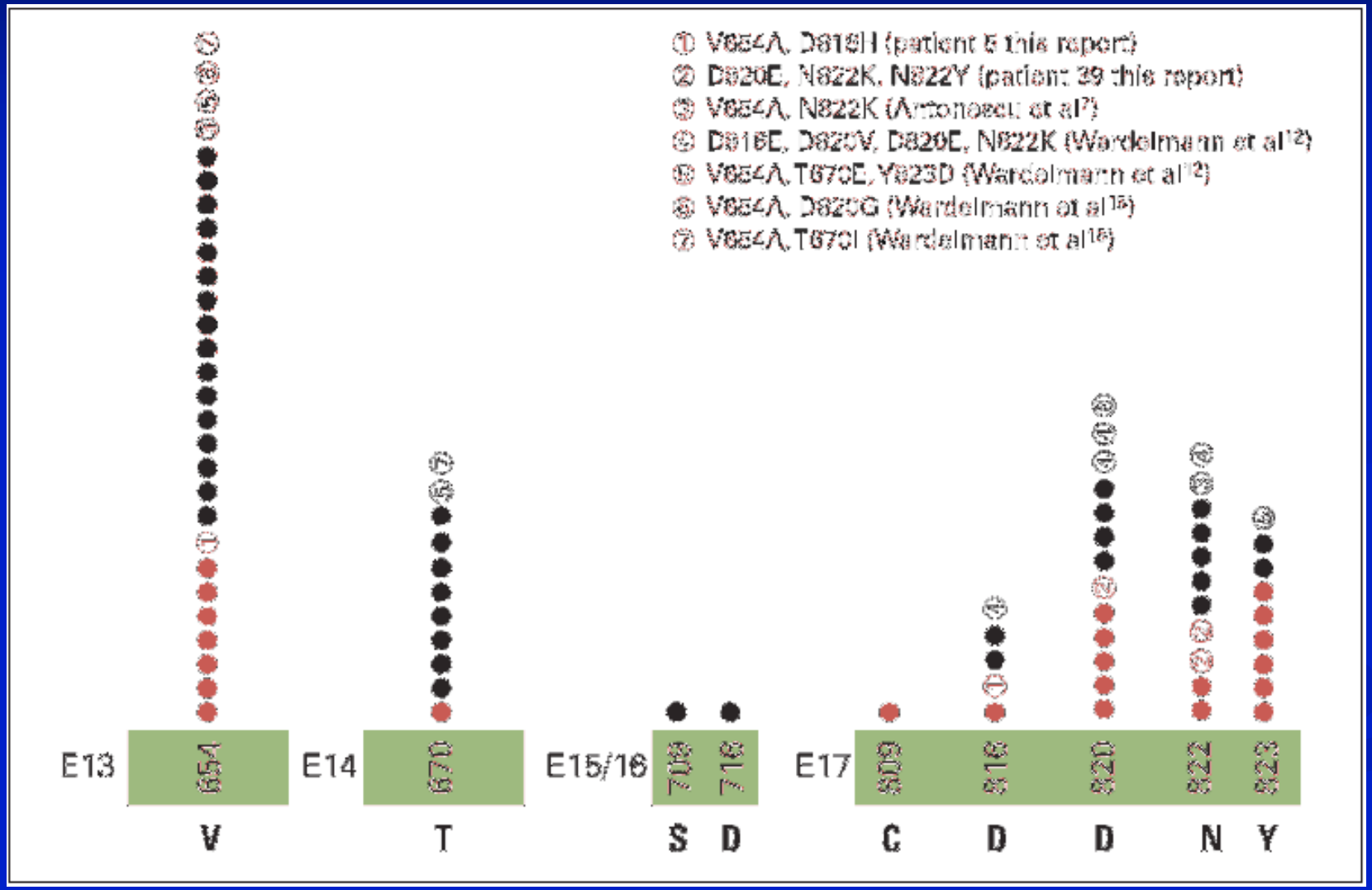
Limited Progression



Resistance to Imatinib Mesylate: Recognition of Clonal Evolution



Secondary Mutation



Heinrich et al, JCO 2006

Should I take imatinib after my GIST was removed?

Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

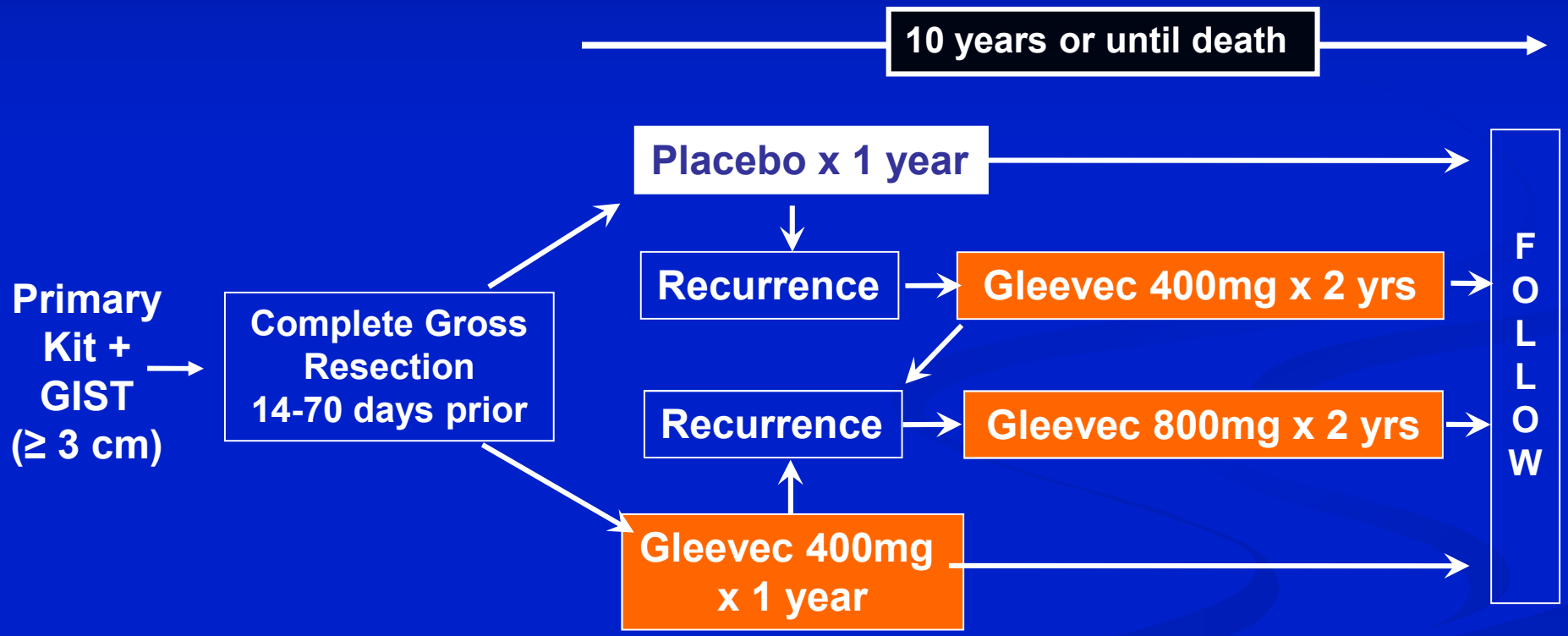
Tumor Parameters		Risk of Progressive Disease (%)			
	Size	Gastric	Duodenum	Jejunum/Ileum	Rectum
Mitotic Index ≤ 5 per 50 hpf	≤ 2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	> 2 ≤ 5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	> 5 ≤ 10 cm	Low (3.6%)	(Insuff. data)	Moderate (24%)	(Insuff. data)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

Data based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
#Defined as metastasis or tumor-related death. *Denotes small numbers of cases.

1. Demetri et. al. *J Natl Compr Canc Netw*. 2007 Jul;5 Suppl 2:S1; 2. Miettinen et. al. *Am J Surg Pathol*. 2005 Jan;29(1):52;
3. Miettinen et. al. *Am J Surg Pathol*. 2006 Apr;30(4):477; 4. Miettinen et al. *Semin Diagn Pathol*. 2006 May;23(2):70.

ACOSOG Phase III Trial

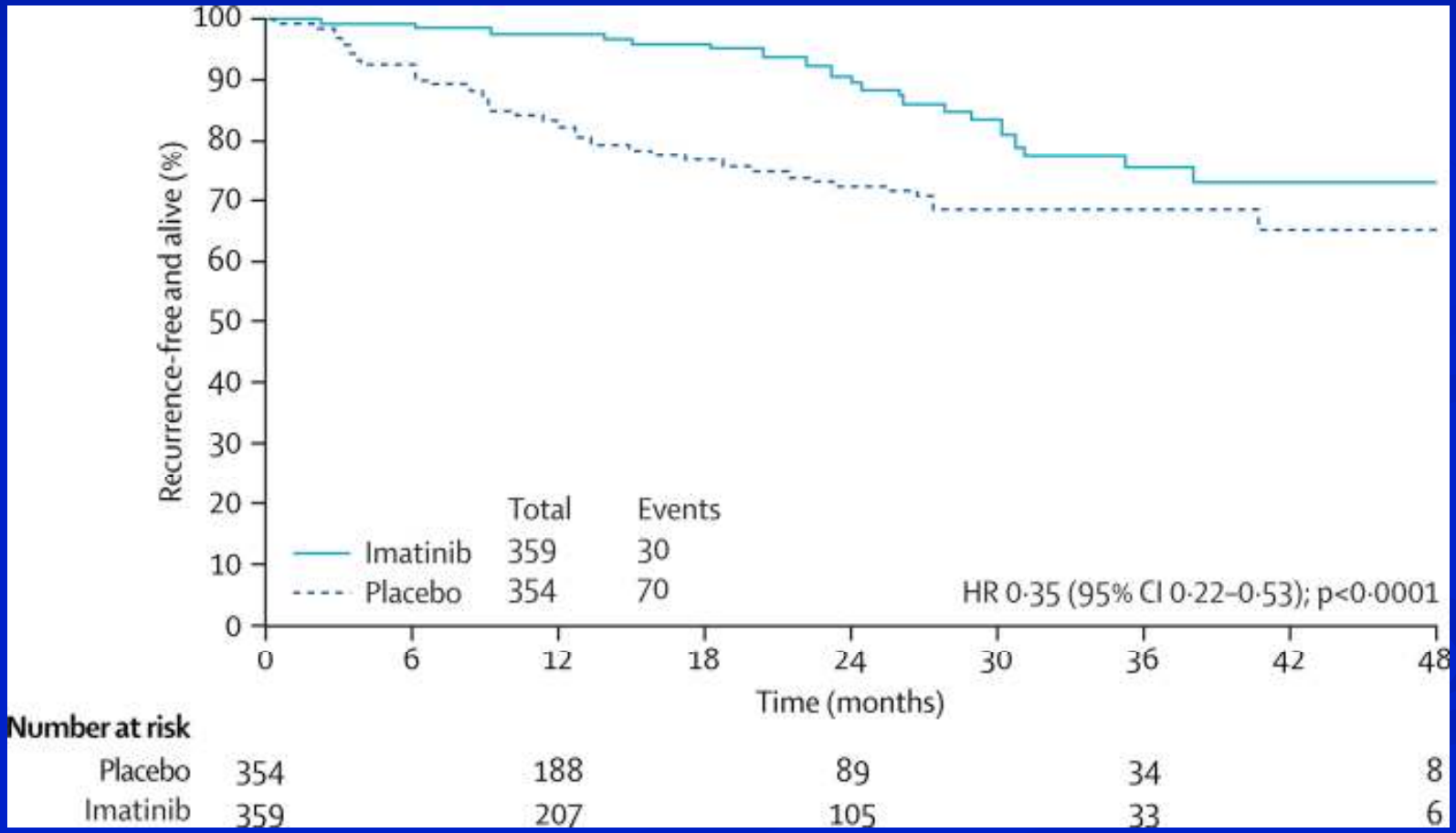
Adjuvant Imatinib in Patients with High Risk Primary GIST



Primary Objective: Recurrence Free Survival (RFS)

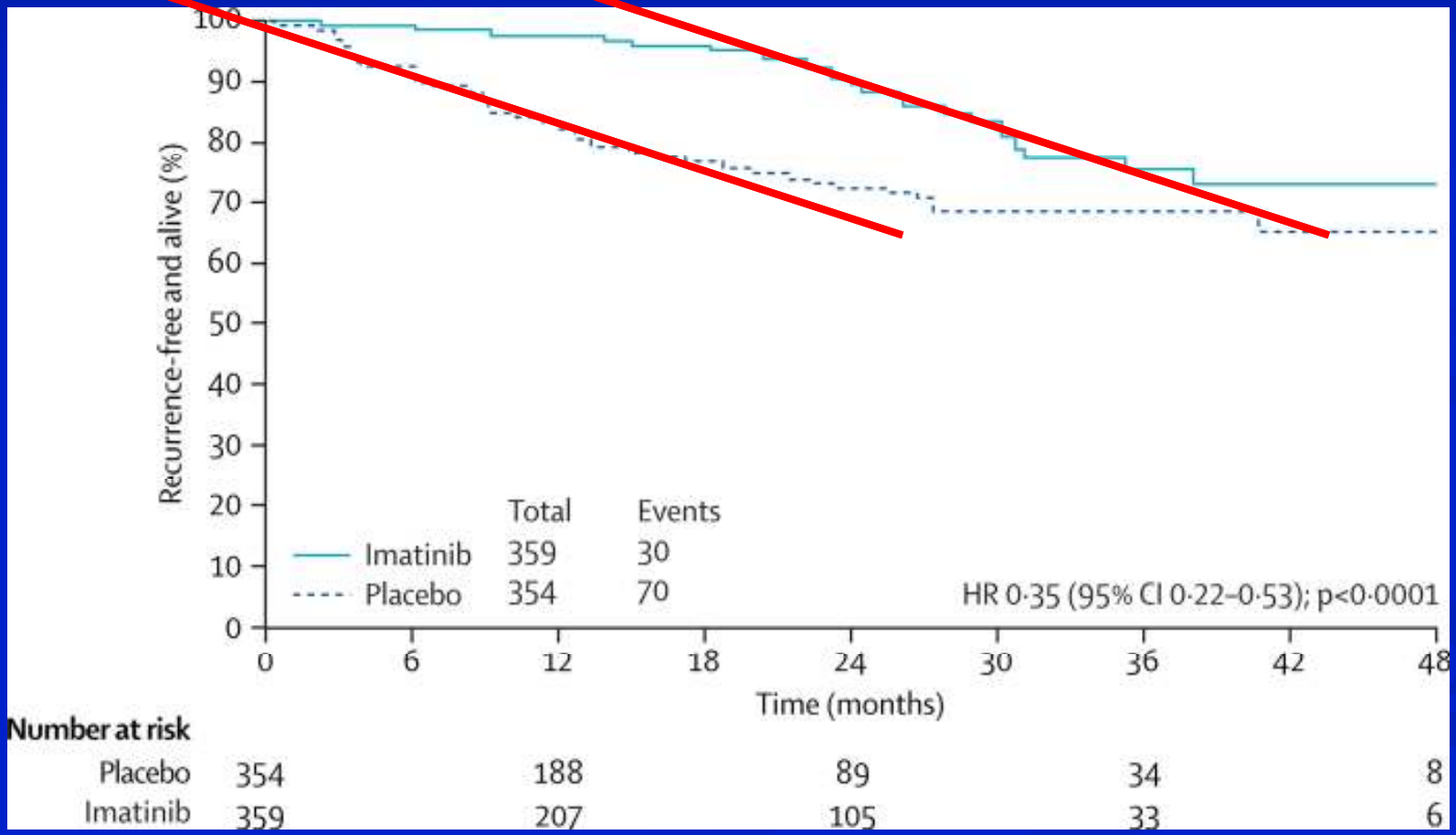
American College of Surgeons Oncology Group. Sarcoma Organ Site Committee. Available at: http://www.acosog.org/studies/synopses/Z9001_Synopsis.pdf.

Adjuvant Imatinib

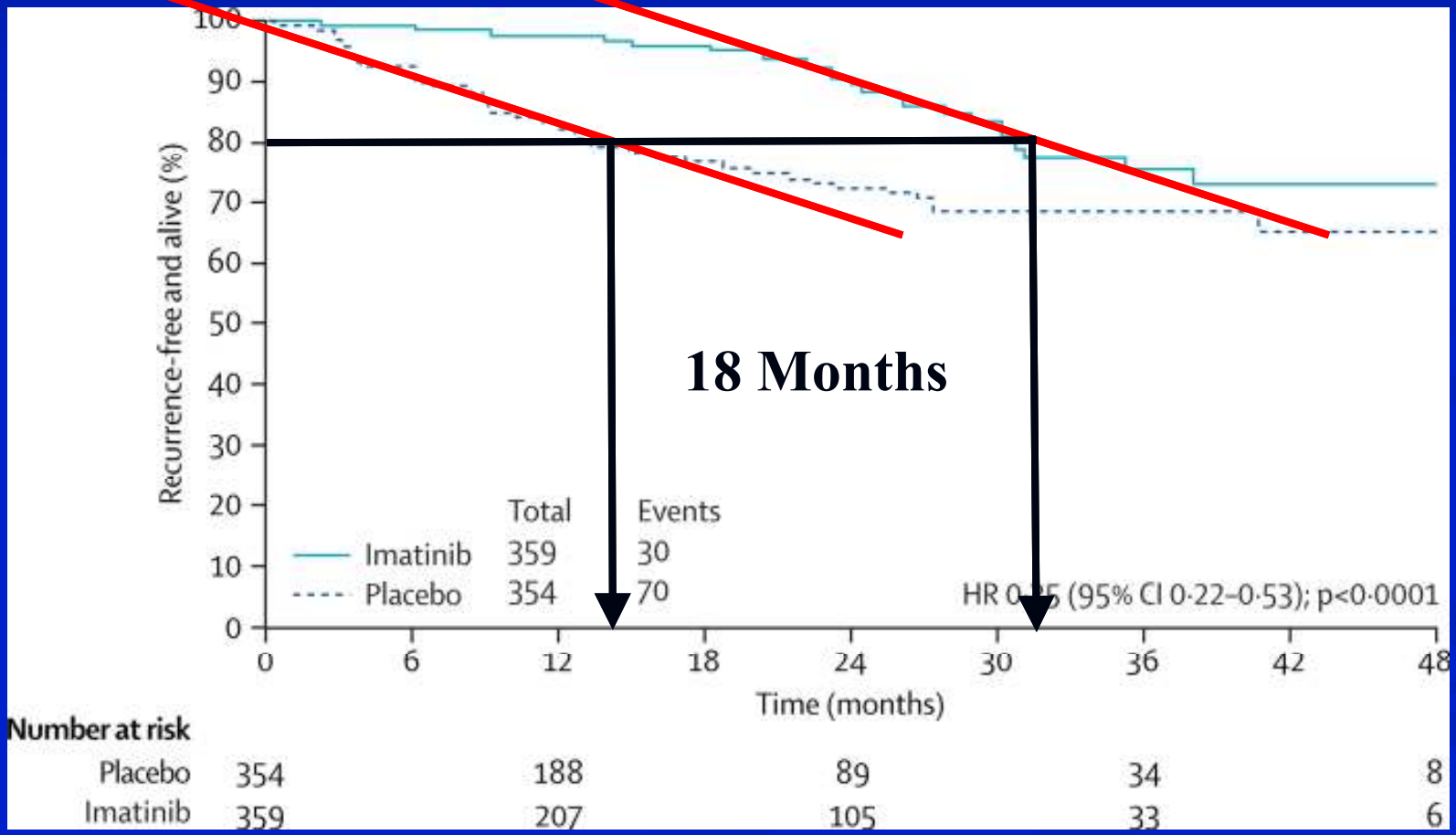


Dematteo Lancet. 2009 Mar 28;373(9669):1097-104. Epub 2009 Mar 18

Adjuvant Imatinib



Adjuvant Imatinib



Postoperative Imatinib Studies

Postoperative Imatinib Trial	Recurrence-Free Survival at 1 y	Recurrence-Free Survival at 2 y
ACOSOG Z9001 (Imatinib)	98%	91%
ACOSOG Z9001 (Placebo)	83%	71%
MDACC-0023 (ITT)	94%	87%
MDACC-0023 (completed 2 y)	**100%**	**100%**

DeMatteo et al. *Lancet.* 2009;373:1097; Blackstein et al. ASCO Gastrointestinal Cancers Symposium, 2010. Abstract 6 and oral presentation; McAuliffe et al. *Ann Surg Oncol.* 2009;16:910.

Other Ongoing Adjuvant Trials in GIST (2010)

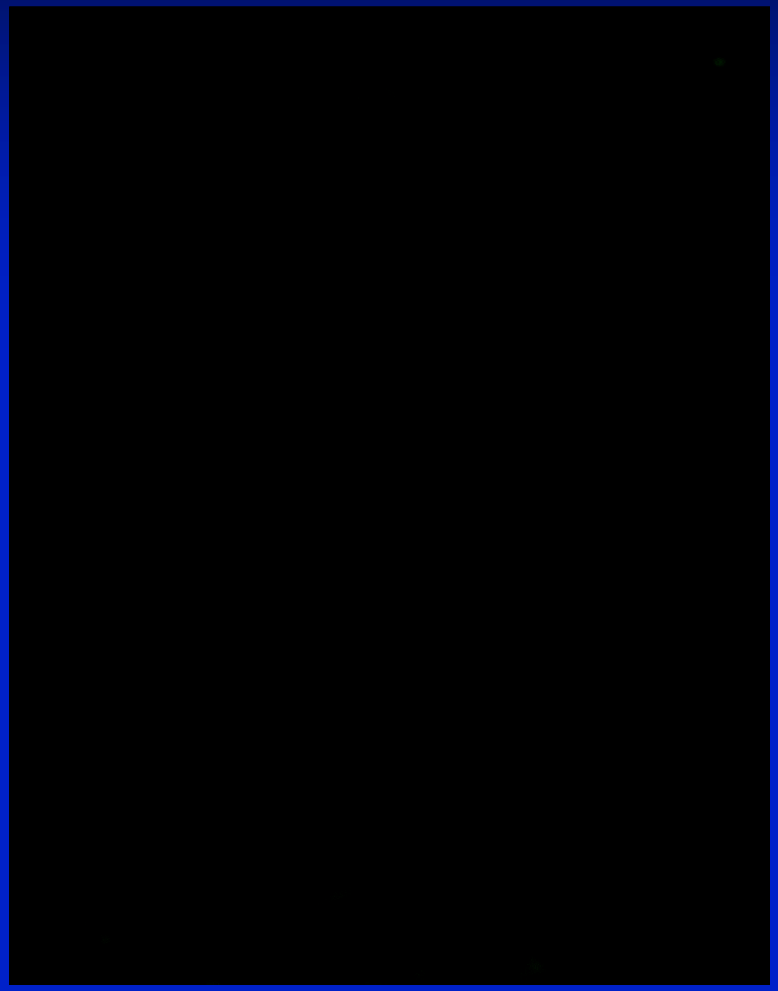
Study (Planned Accrual)	Inclusion*	Treatment/ Primary Endpoint
SSG XVIII [NCT00116935] Phase 3 (N=400)	>10 cm or mitoses >10 >5 cm + mitoses >5	1 vs 3 y imatinib RFS
EORTC-62024 [NCT00103168] Phase 3 (N=750)	>5 cm or mitoses >10 <5 cm + mitoses 6-10	0 vs 2 y imatinib OS
CSTI571BUS282 [NCT00867113] Phase 2 (N=133)	≥2 cm + mitoses ≥5 (≥5 cm only for non-gastric GIST)	5 y imatinib Time to recurrence

*Tumor size in cm; number of mitoses per 50 HPFs.

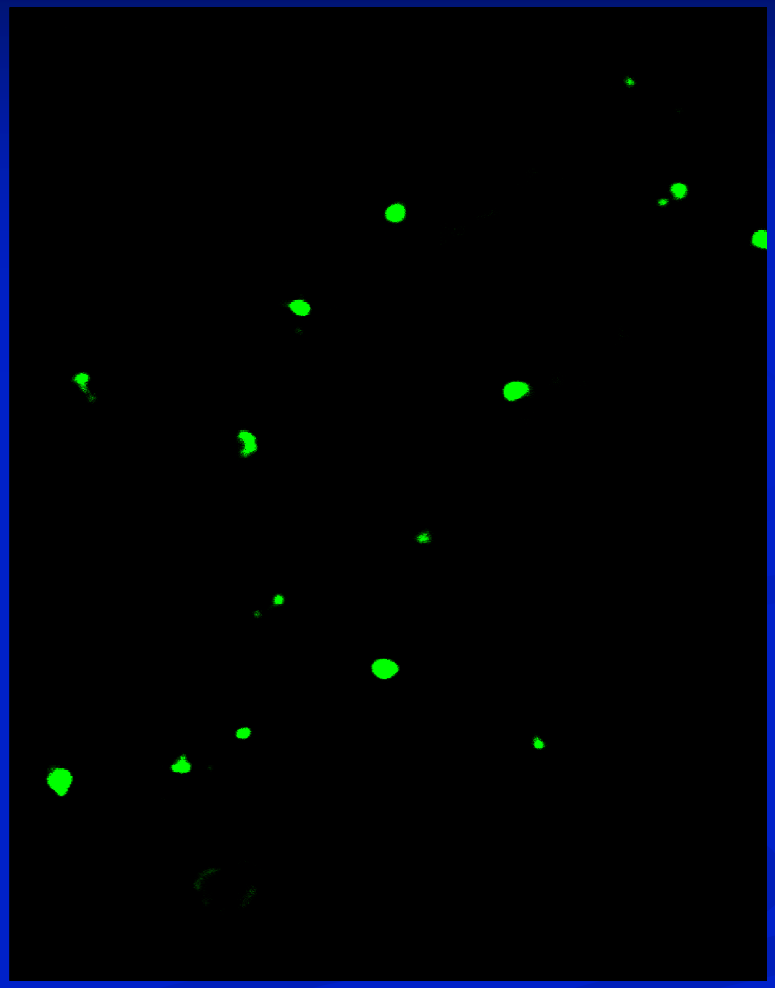
SSG = Scandinavian Sarcoma Group.

Gold and DeMatteo. *Ann Surg.* 2006;244:176; http://clinicaltrials.gov. Accessed April 2010.

Effect of Imatinib on Apoptosis



Pre-Imatinib

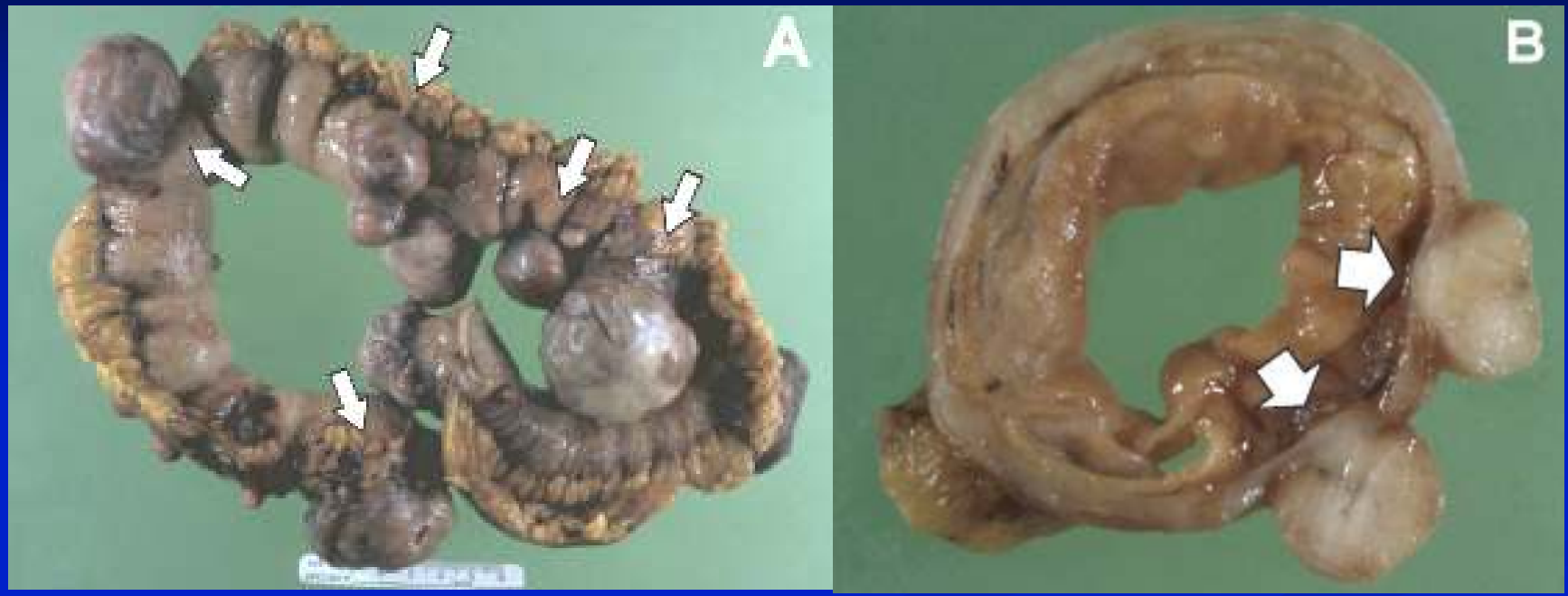


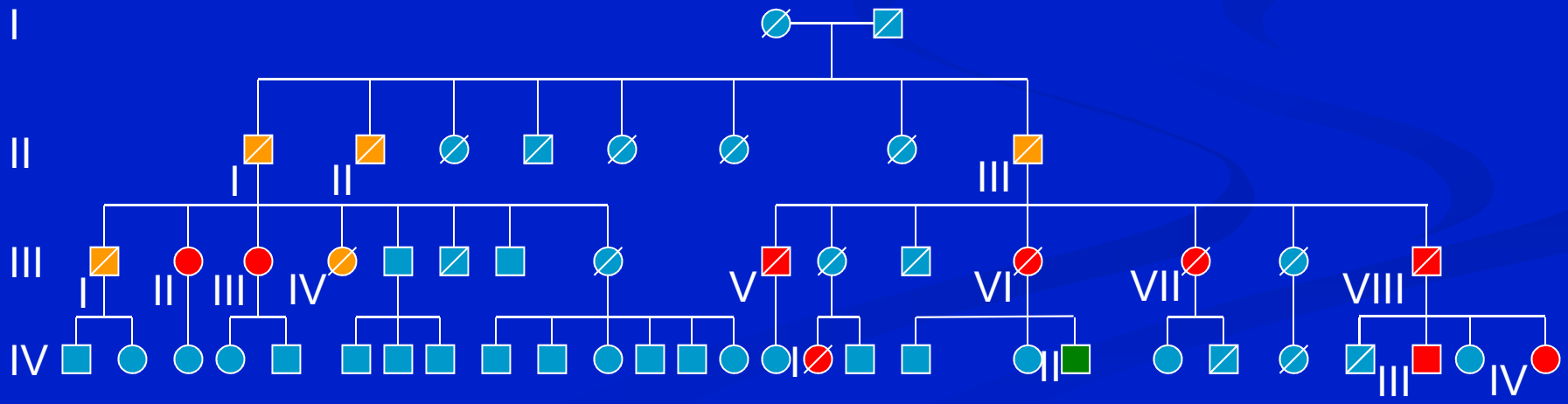
Post-Imatinib
(3 days of therapy)

Immunofluorescent TUNEL Assay

Will my kids get GIST?

Familial GIST





Gastrointestinal Stromal Tumors

GISTS 2010

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