Gastrointestinal Stromal Tumor (GIST)

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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
- About 5,000 newly diagnosed GIST patients per year in the US
- Clinical presentation is variable
  - pain, hemorrhage, anemia, anorexia, nausea, bleeding
- High recurrence rate after surgery (>50%)
- No effective chemotherapy

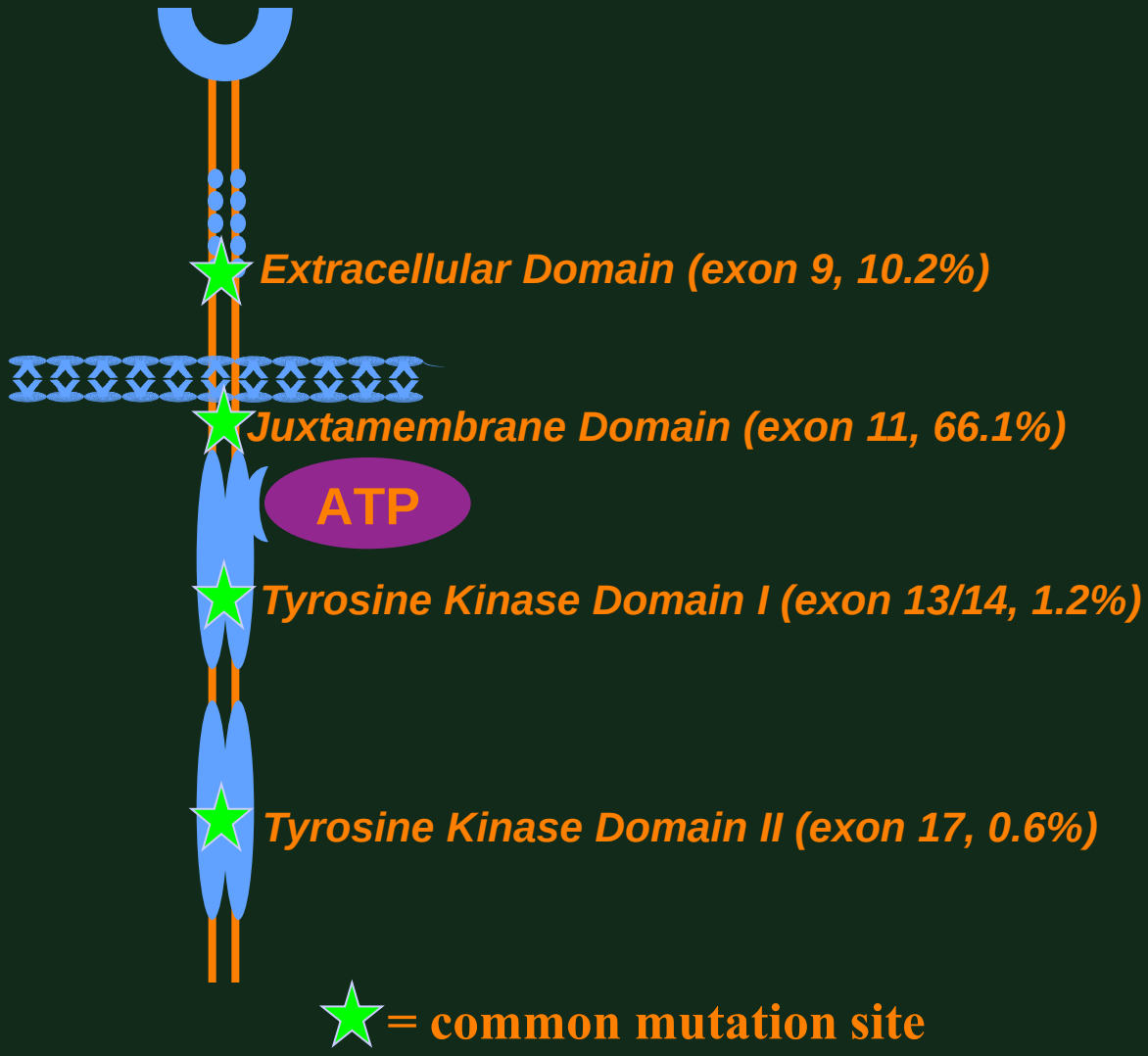
GIST Pathology

- 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

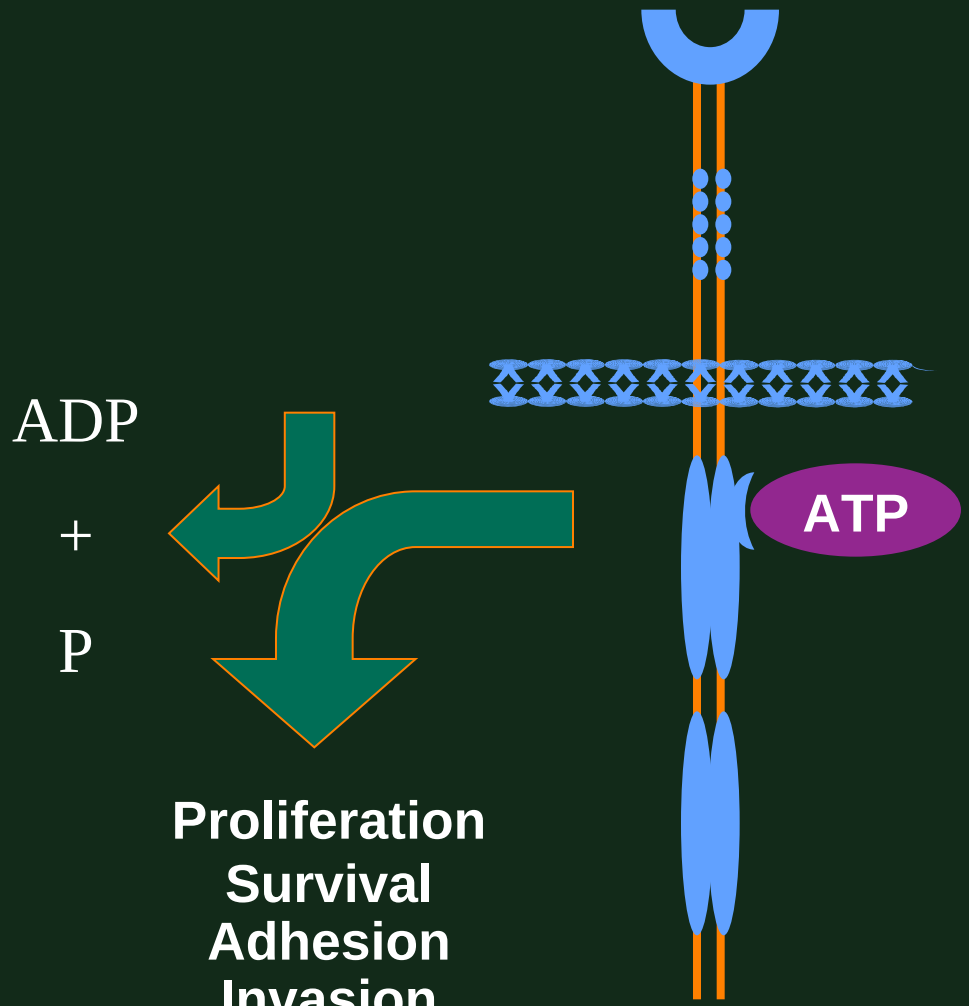
ICC = interstitial cells of Cajal.

Corless et al. *J Clin Oncol*. 2004;22:3813.
Sircar et al. *Am J Surg Pathol.* 1999;23:377.

Kit Receptor Structure

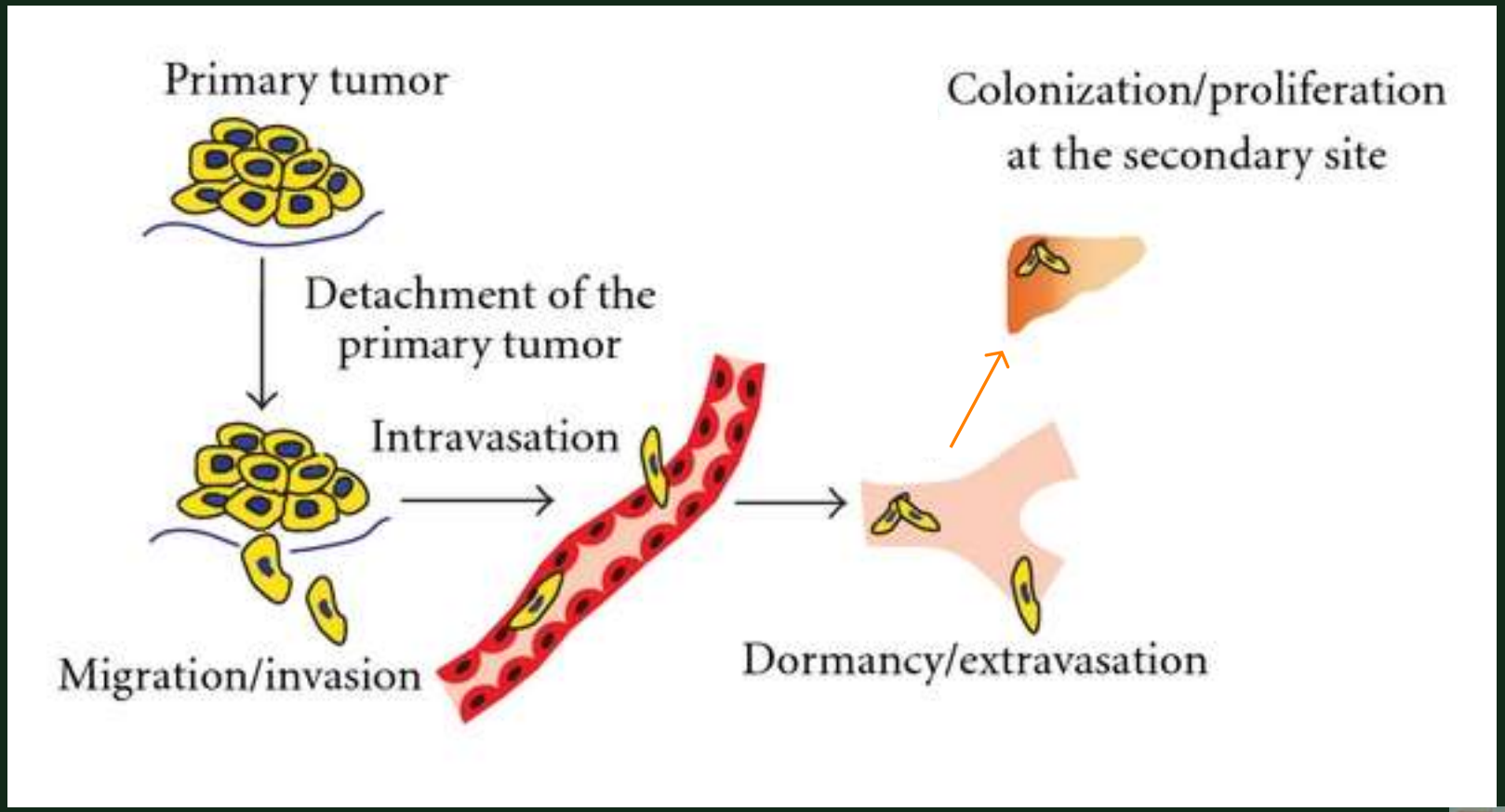


Kit Receptor Phenotype

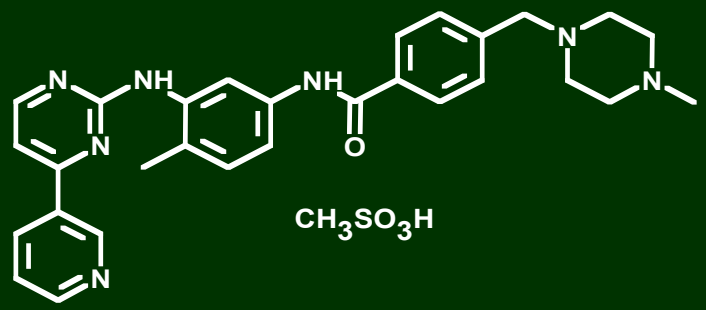


Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

Metastasis in GIST



Imatinib Mesylate



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

MW: 589.7

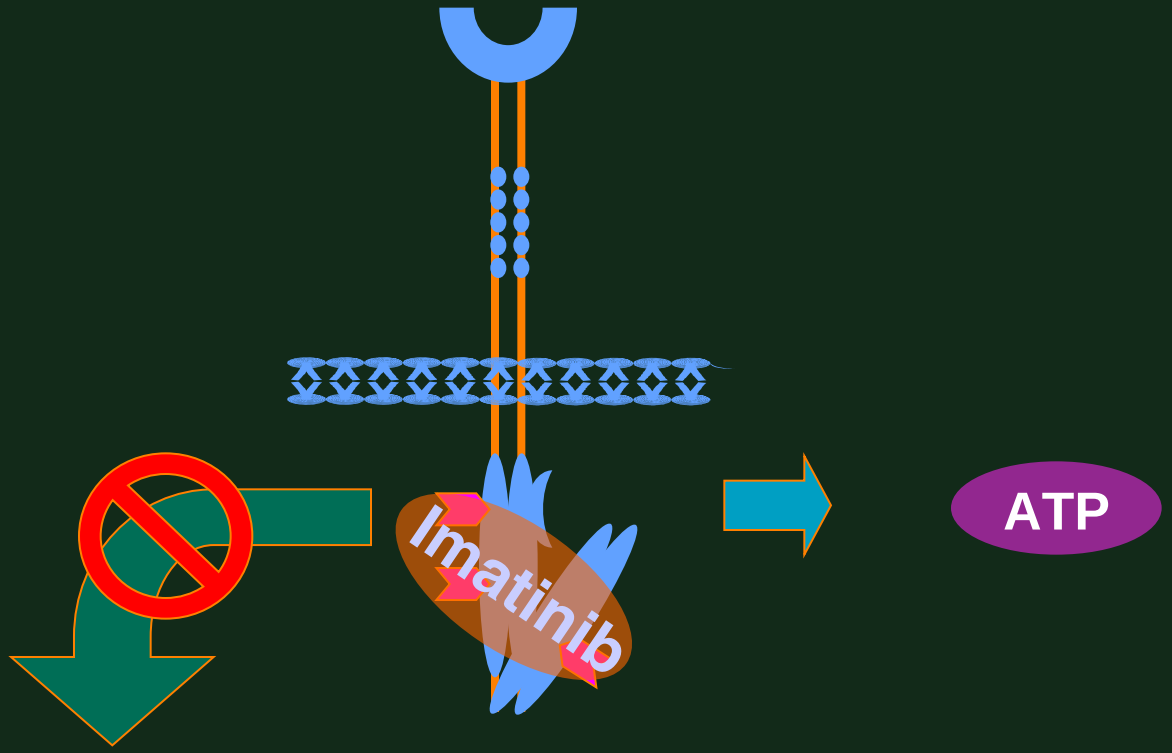
- Rational drug design
  - 2-phenylamino pyrimidine
  - Based on structure of ATP binding site
  - Highly water soluble
  - Oral bioavailability

Inhibitor of selective tyrosine kinases

- bcr-abl
- PDGF-R
- c-kit

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

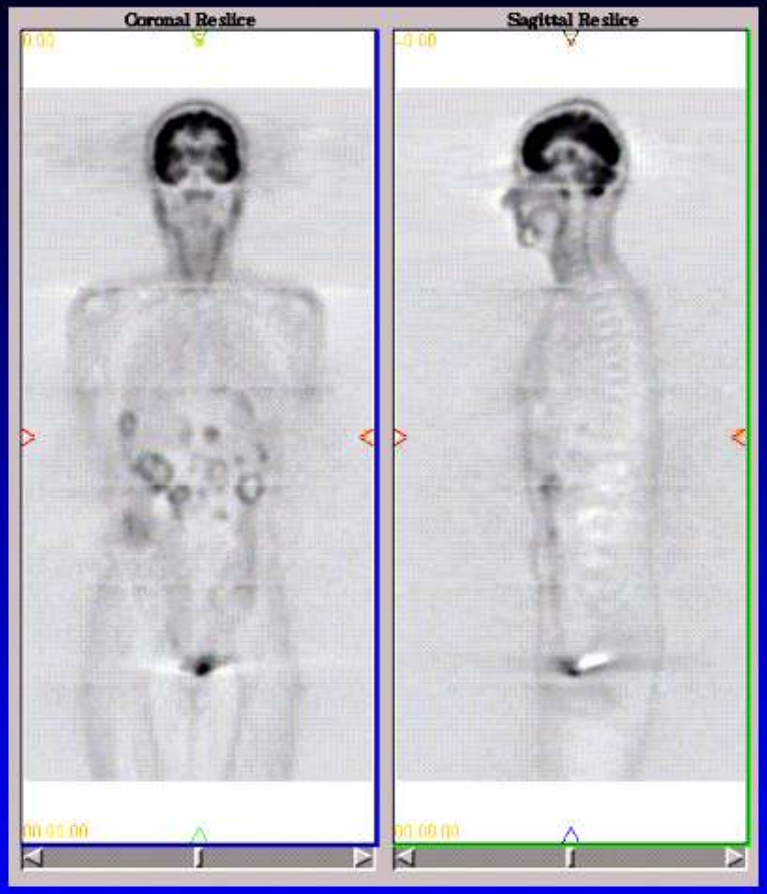
Kit Receptor Phenotype



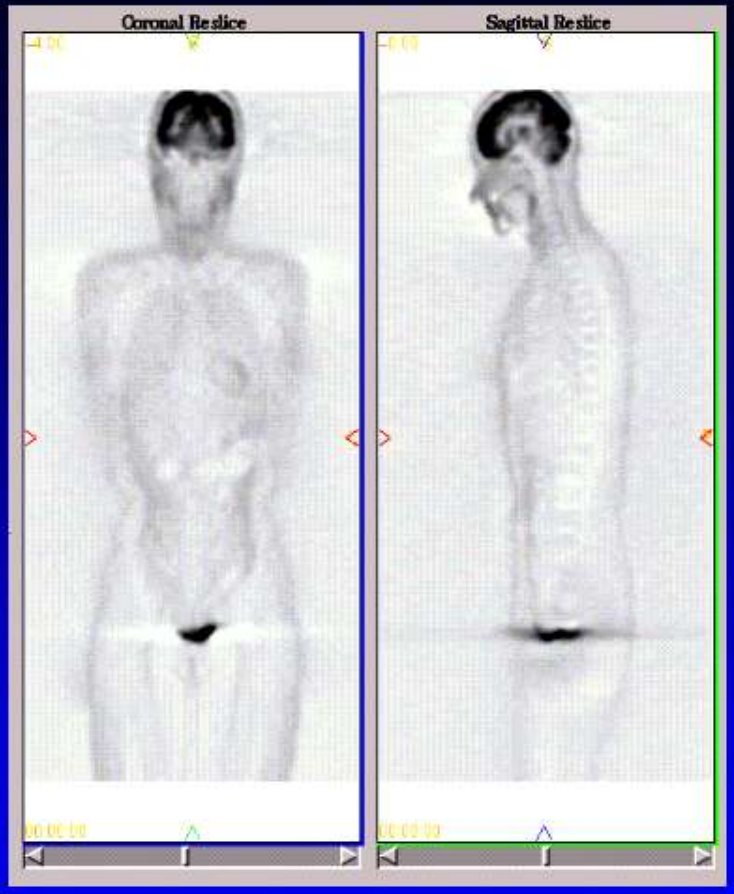
Proliferation
Survival
Adhesion
Invasion
Metastasis
Angiogenesis

= 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

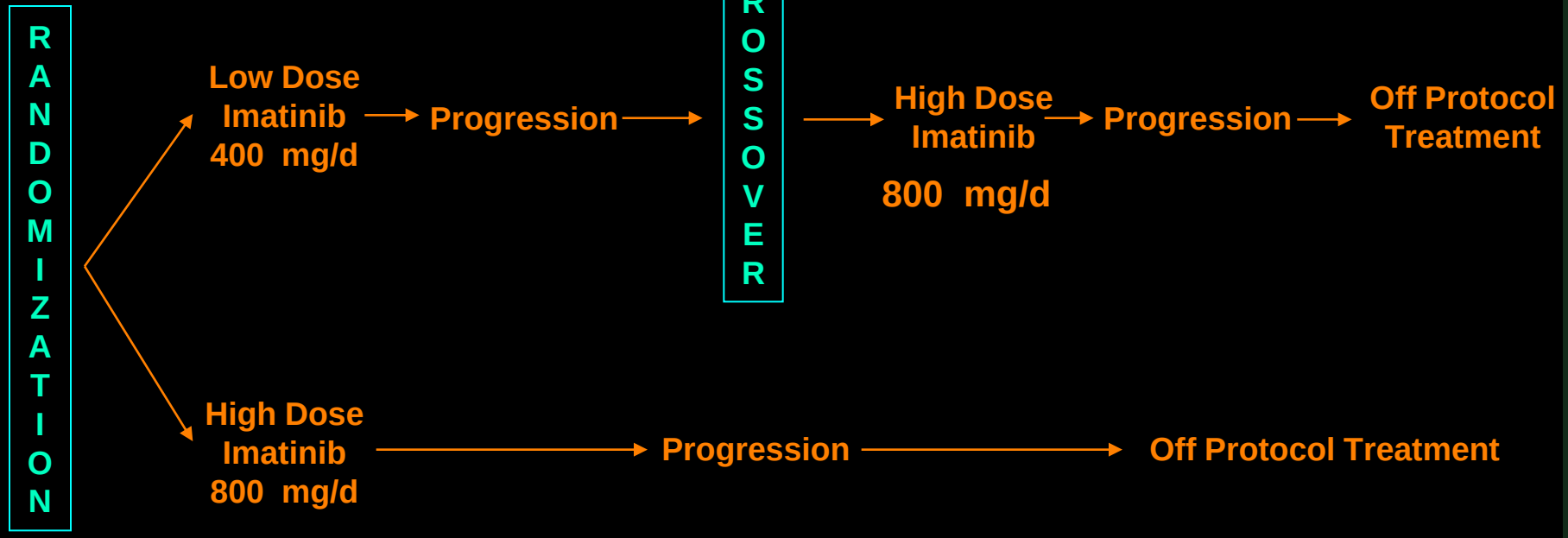
Joensuu H et al. *N Engl J Med.* 2001;344:1052-1056.

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)

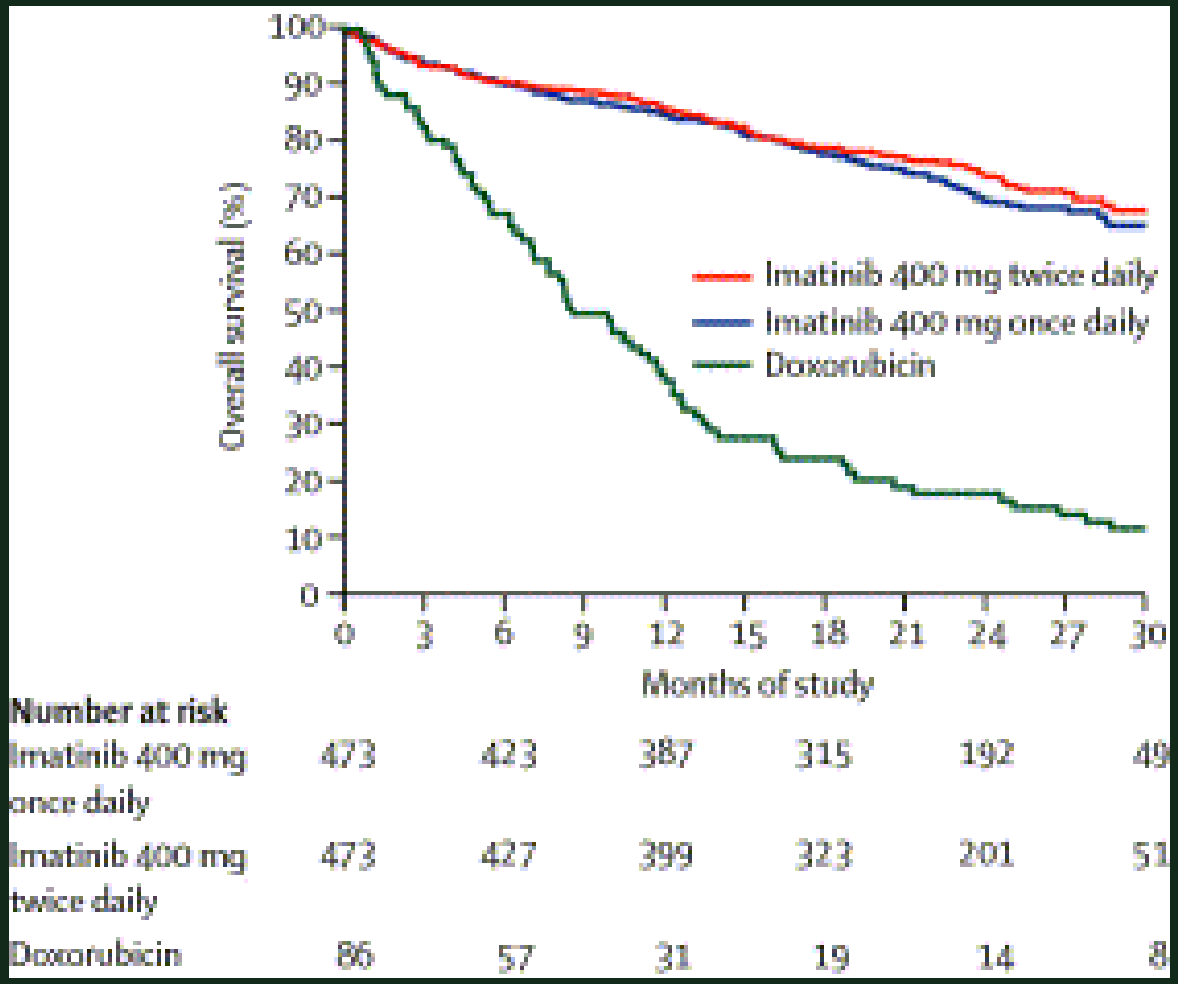
Courtesy Dejka Araujo, M.D.

North American Sarcoma Intergroup
Schema



EORTC Phase III Imatinib for Advanced GIST

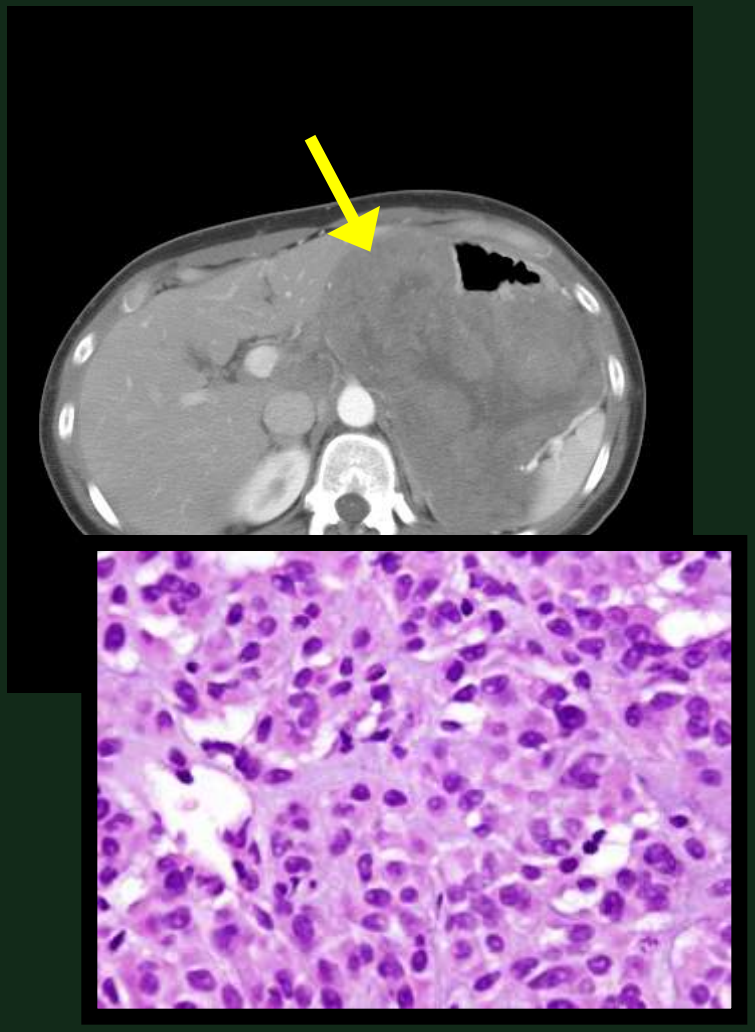
Survival Benefit



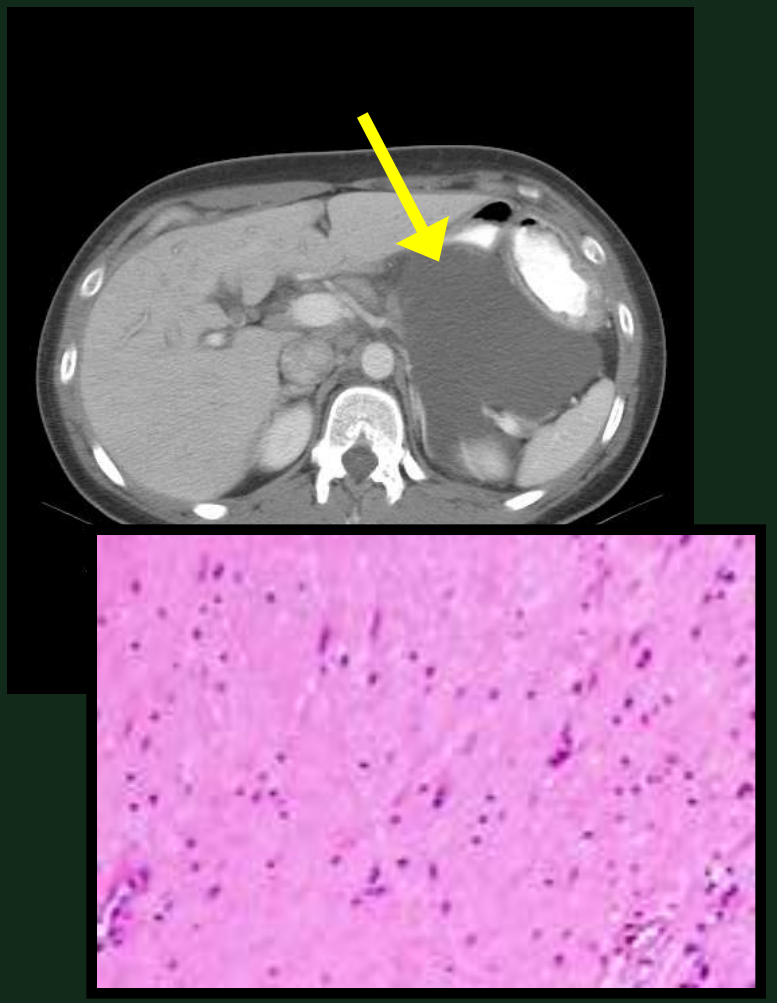
Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Verweij, et al 2004

GIST Response



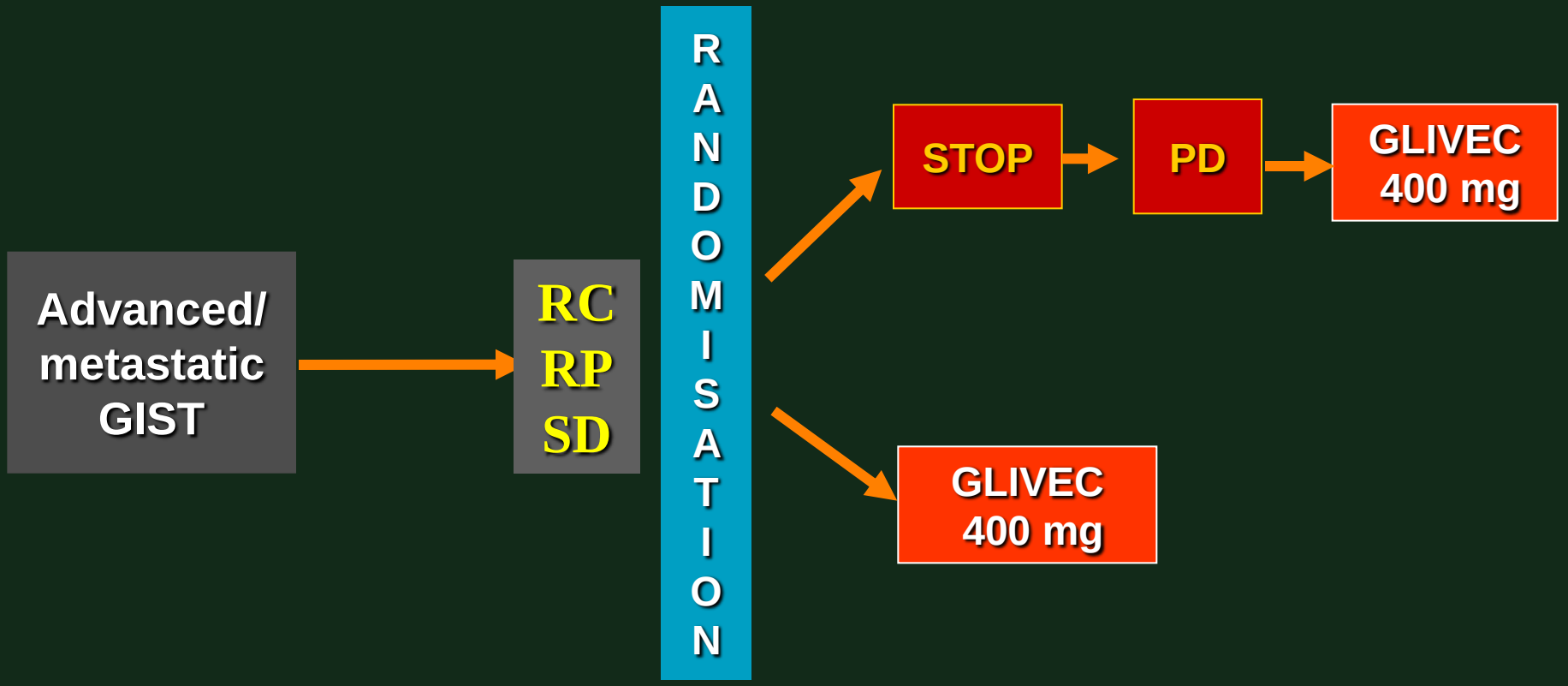
Pre-Imatinib



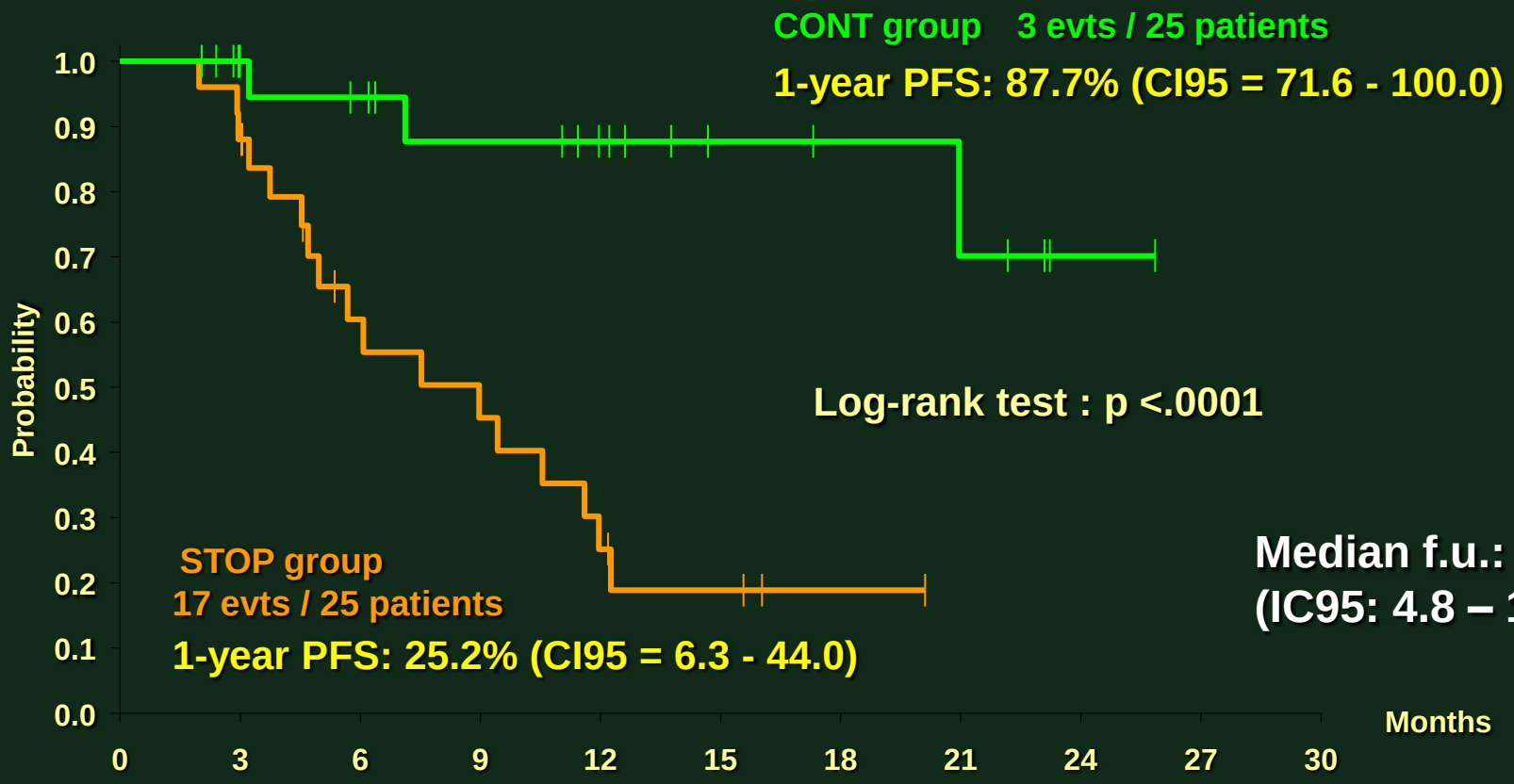
Post-Imatinib (8 weeks therapy)

How Long Do I take Imatinib?

BFR14 3-yr randomization



BFR14 3-yr randomization
Progression Free Survival



Rate of PD in STOP group

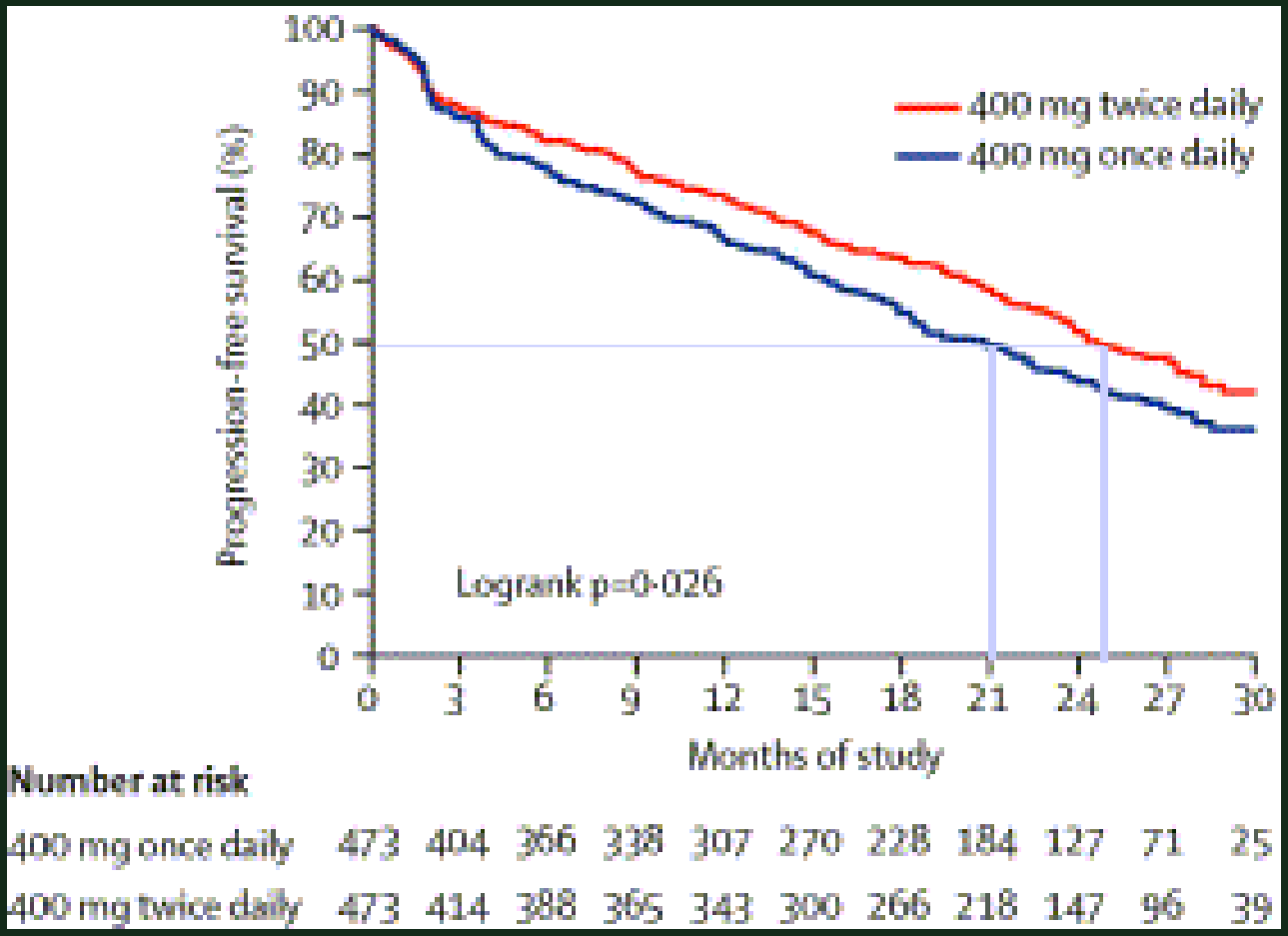
at 6 months: 40%
at 9 months: 55%
at 1 year: 75%

Updated sept 07, ECCO 14

What Dose of Imatinib Do I Take?

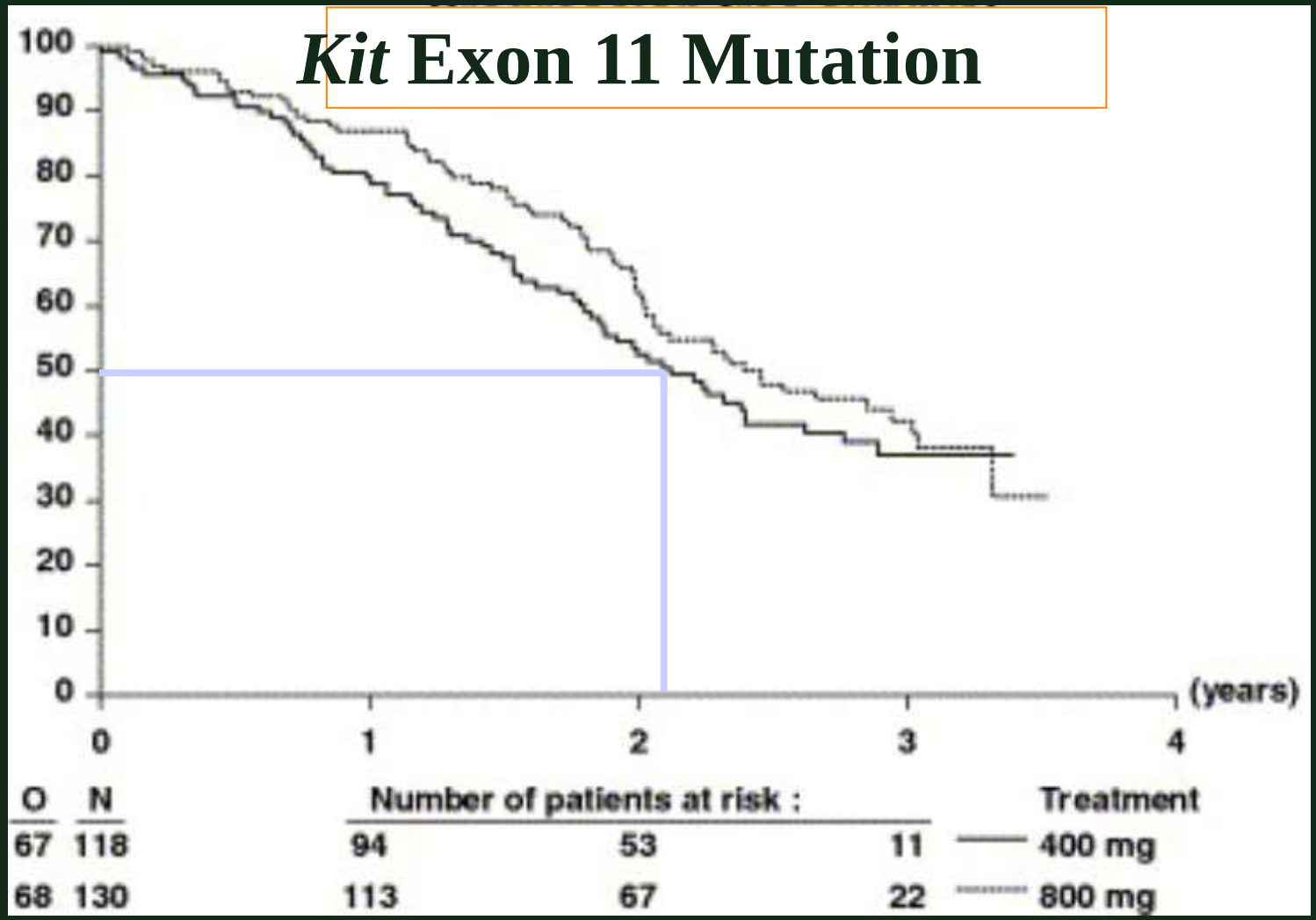
EORTC Phase III Imatinib for Advanced GIST

Progression-free Survival Benefit



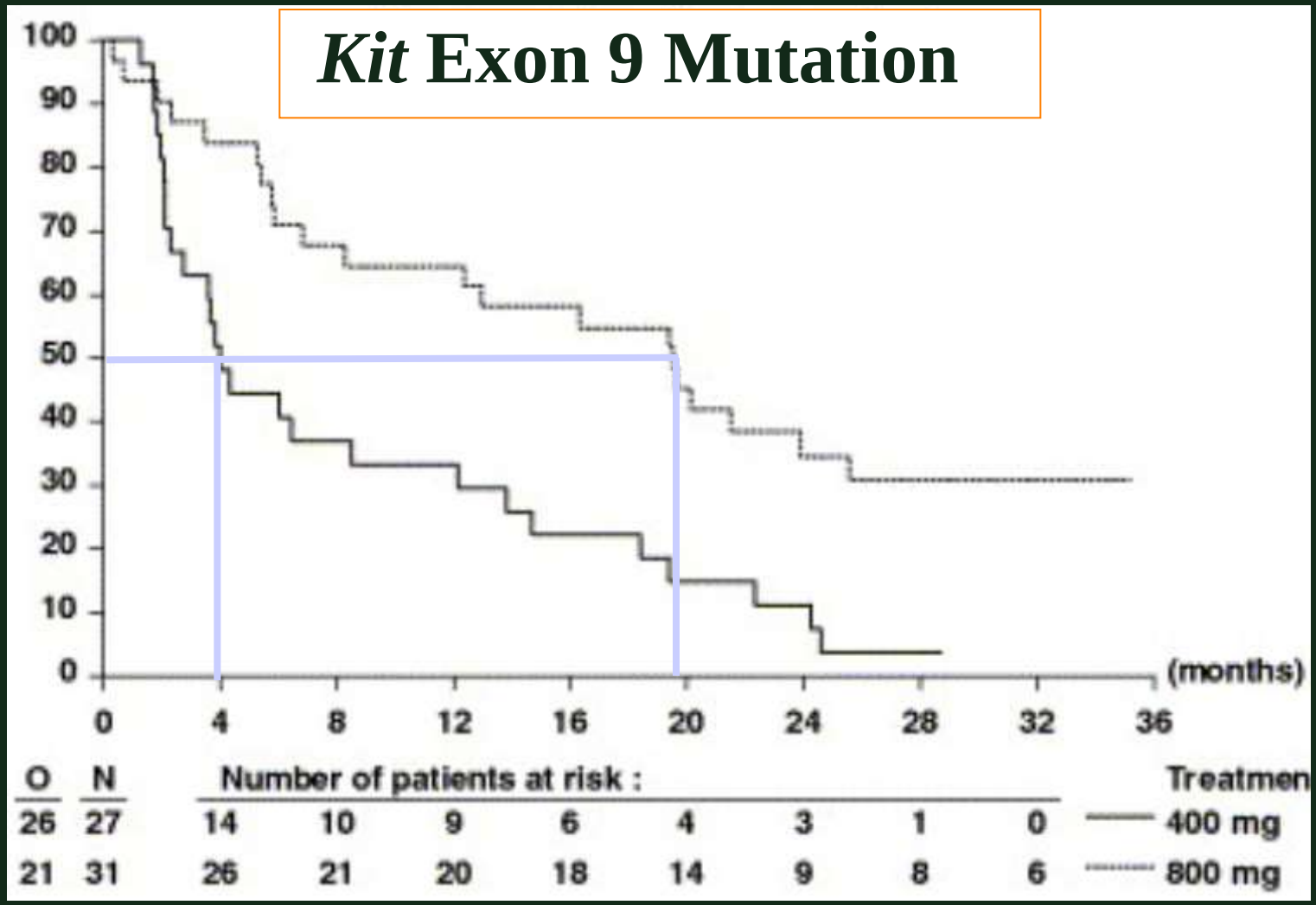
Verweij, et al 2004

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 200

Progression-free Survival By Imatinib Dose



Debiec-Rhycter et al, 200

Will I Have Side Effects?

How Do I Manage Them?

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

Is My GIST "Responding" To Therapy

Radiographic Efficacy

Confirmed Overall Responses with Gleevec

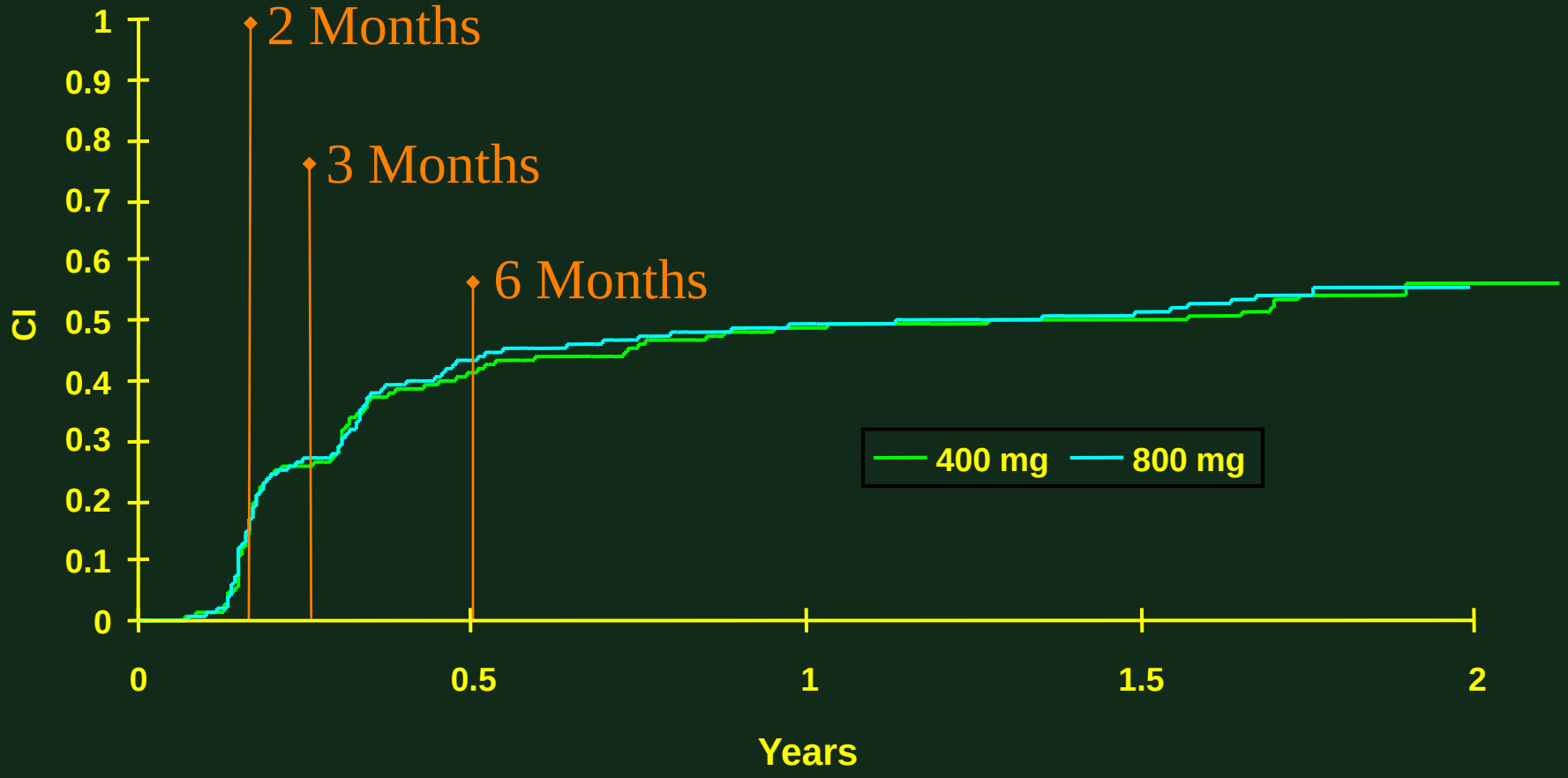
Total patients	N	Confirmed partial response (%)	95% Confidence Interval
400mg	73	33	22-45
600mg	74	43	32-55
Total	147	38	30-46

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

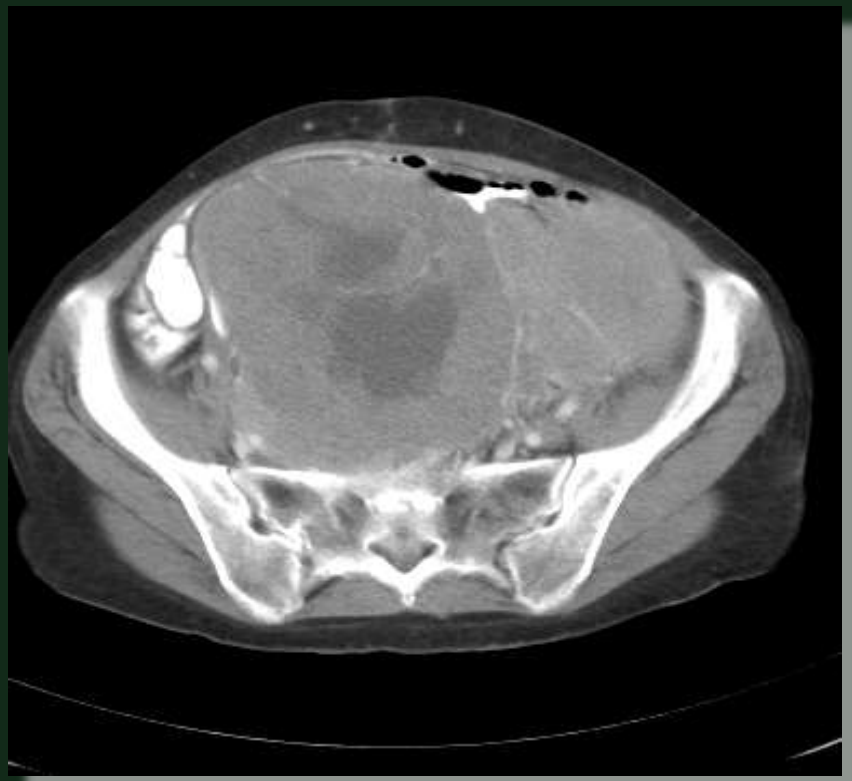


Verweij et al, ASCO 2003

Good “Response”

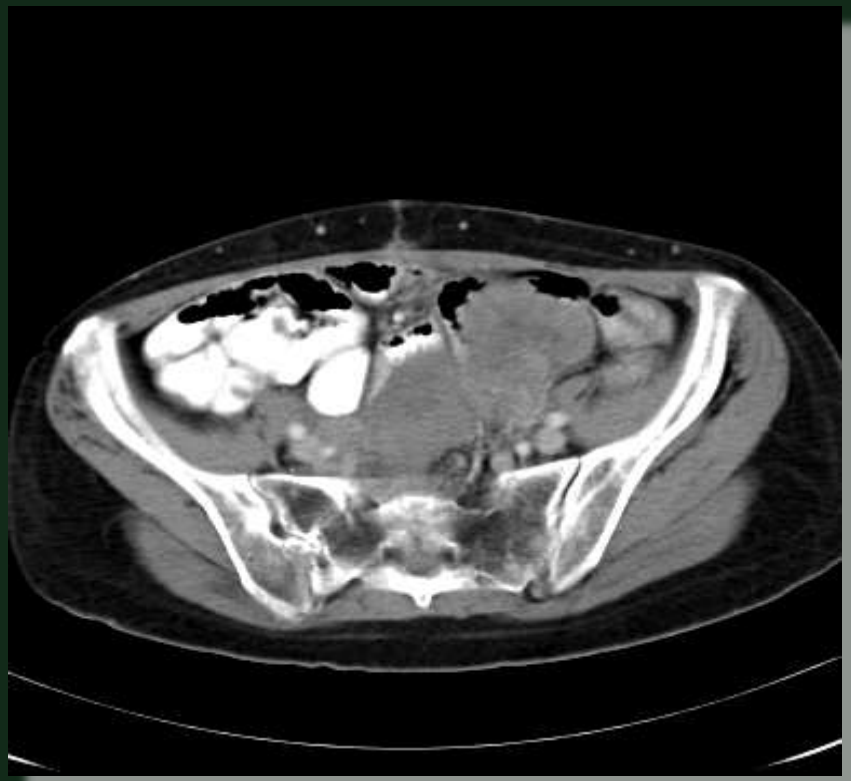
CT Scan Results

Jun 27, 2000



Before Imatinib

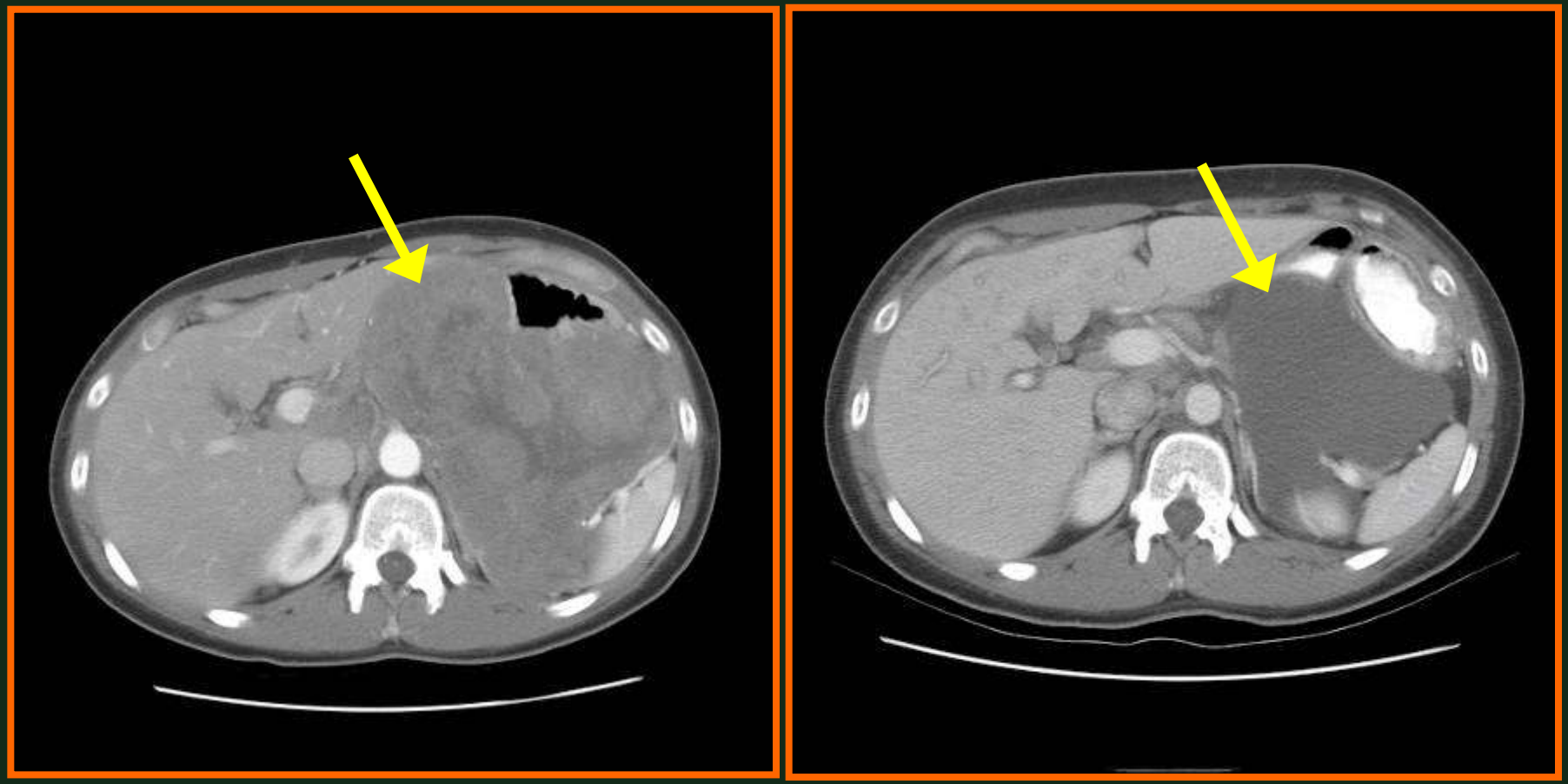
Oct 4, 2000



After Imatinib

Good “Response”

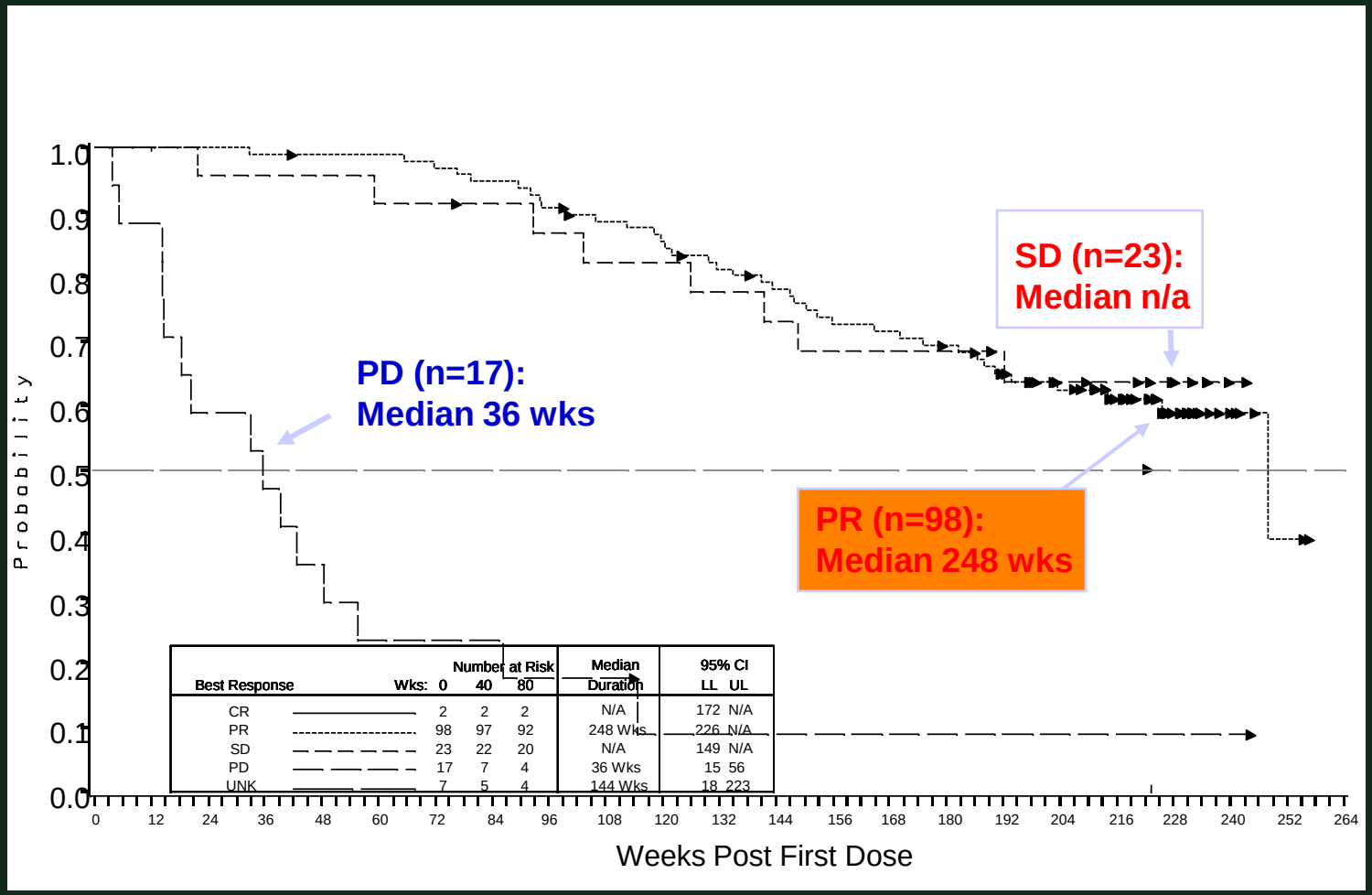
CT Scan Results



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

Survival by Best Response

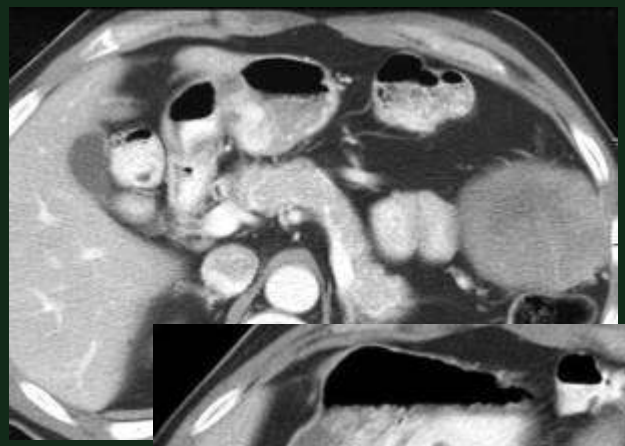
(B222, Kaplan Meier Estimate)



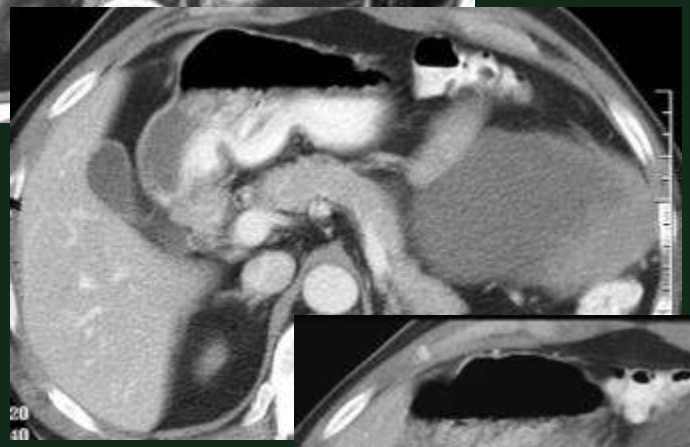
[CR (n=2; median OS n/a) and unknown/NE (n=7; median OS 144 wks) not included]

Paradoxical Good "Response"

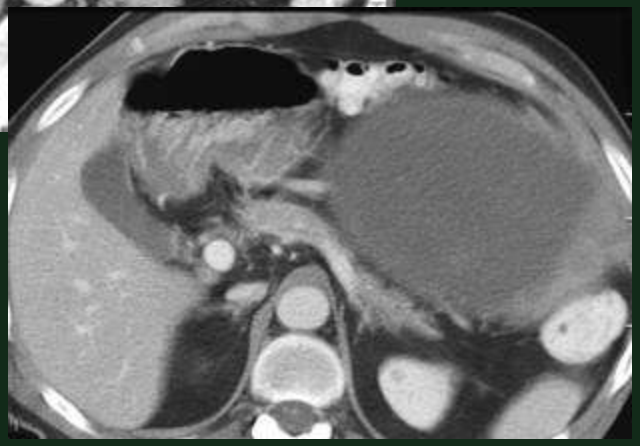
CT and PET findings



1/18



3/23

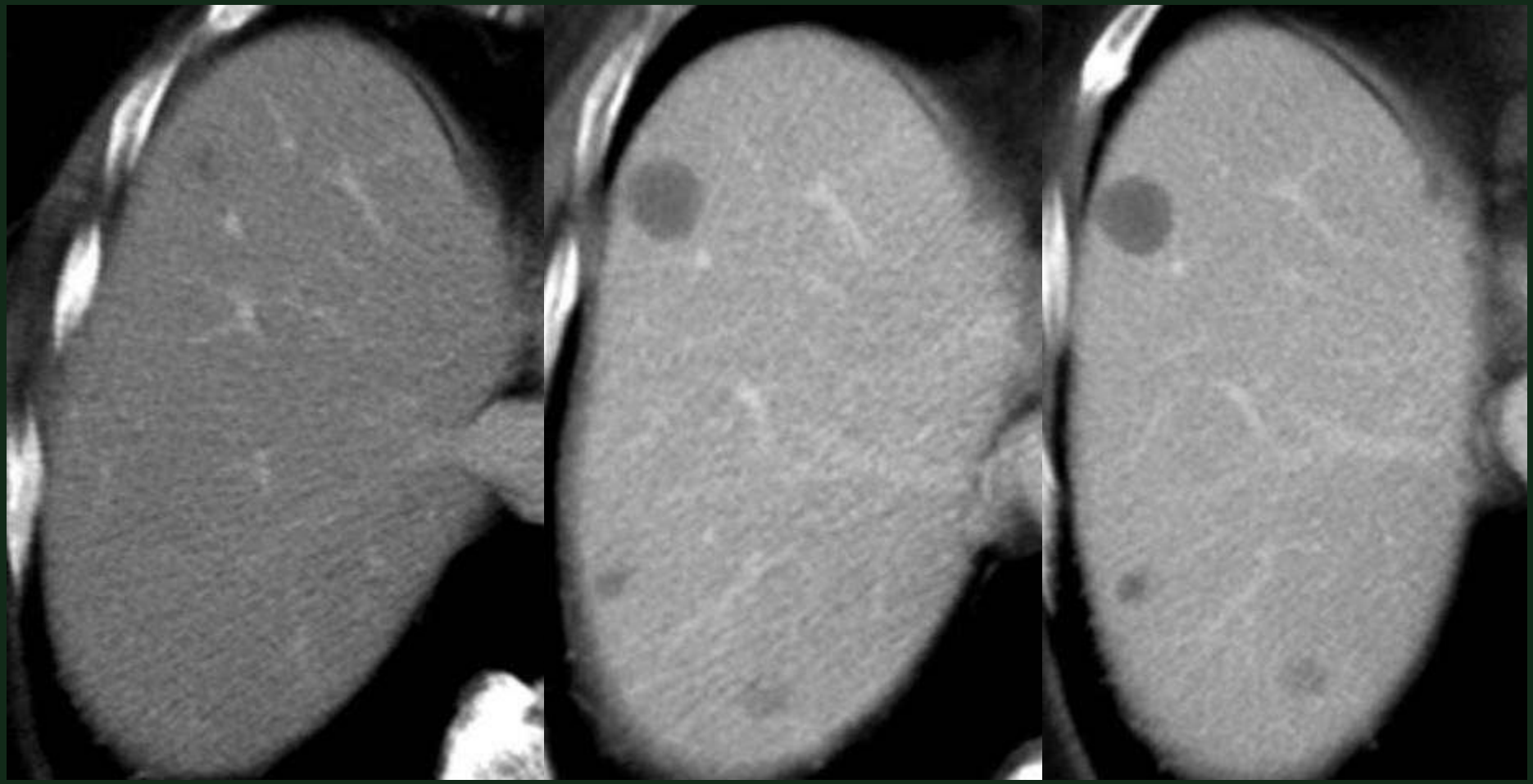


10/8

1/26

3/22

Paradoxical Good "Response"
CT and PET findings

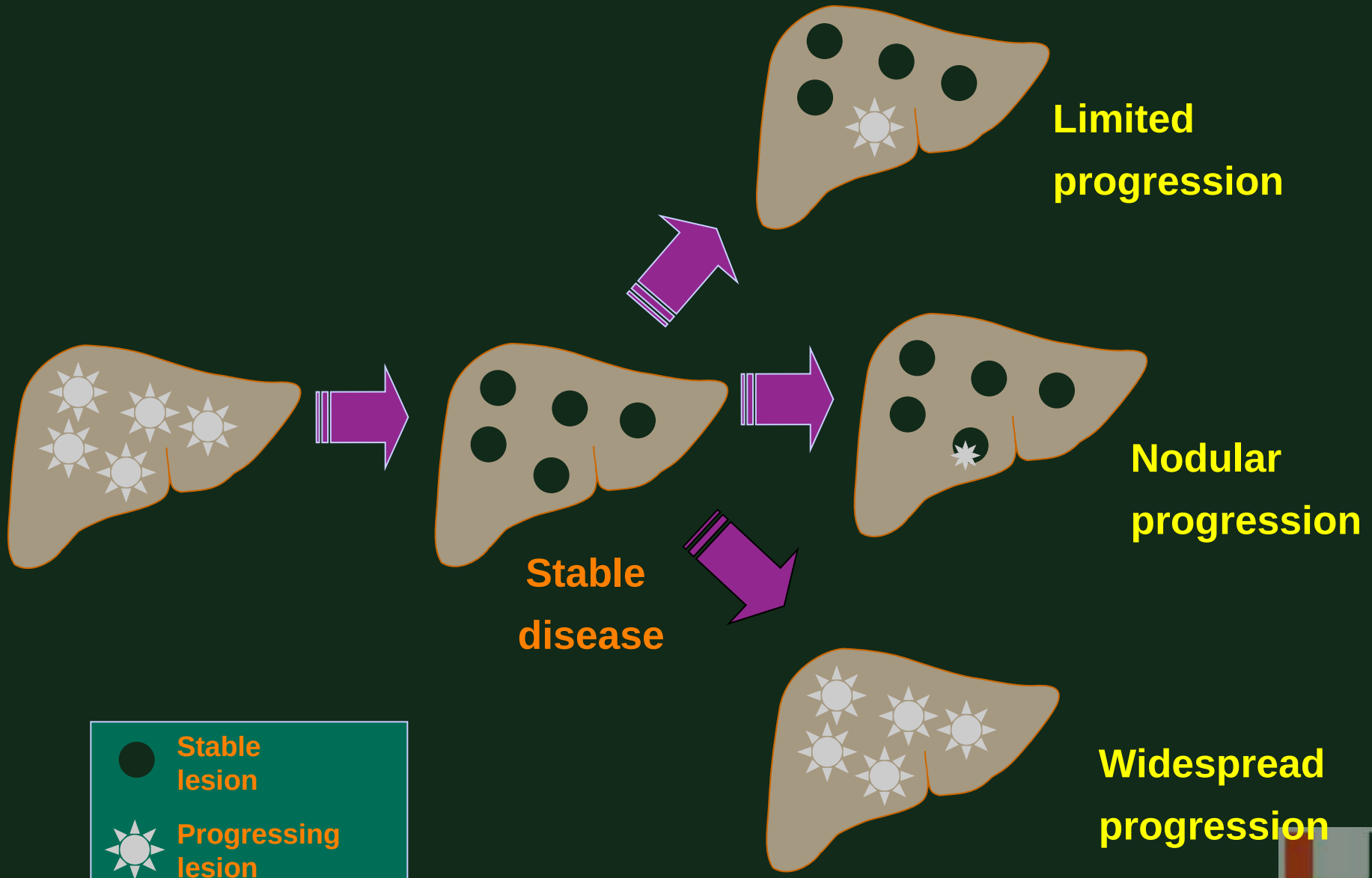


1/12 3/30 5/24

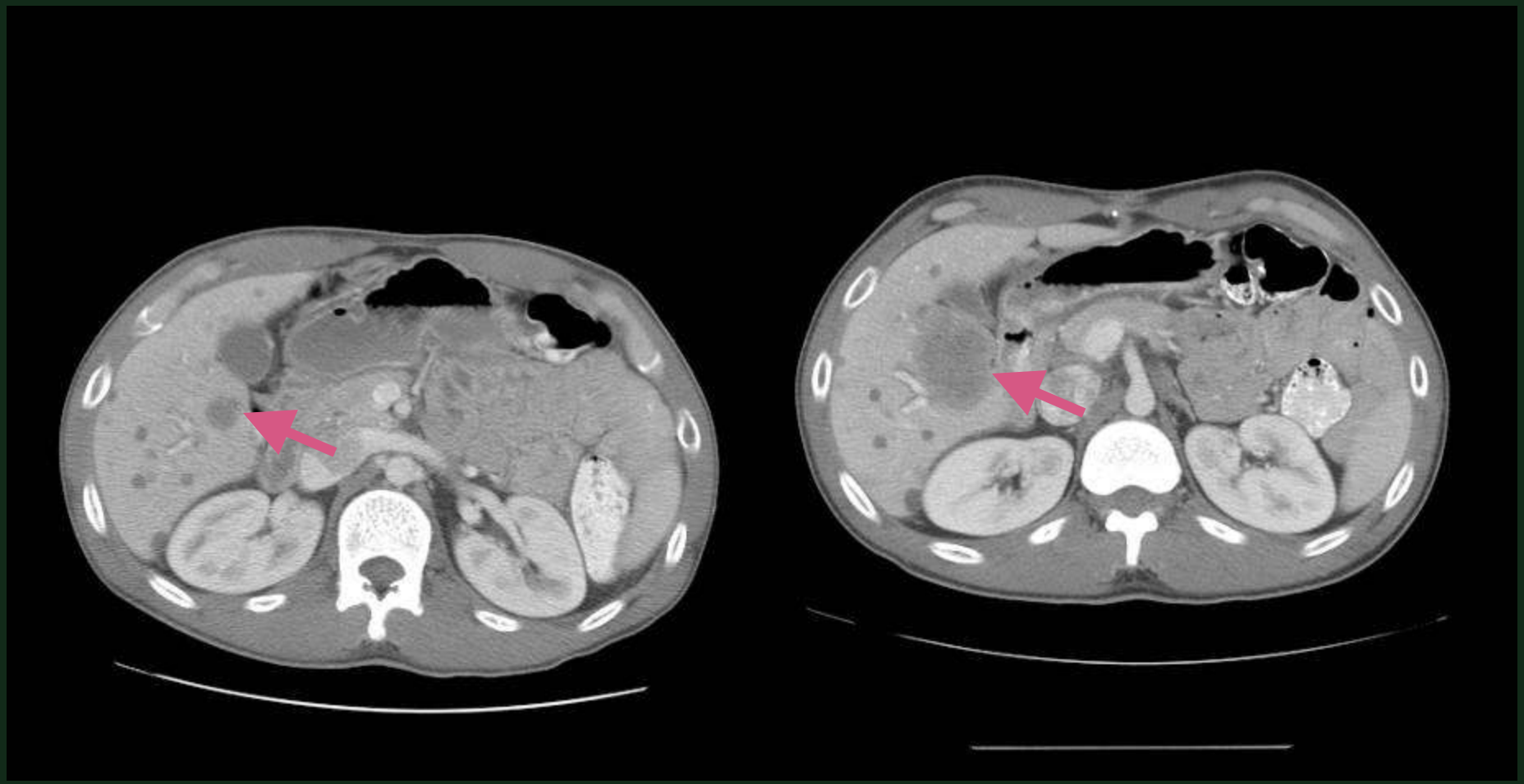
Who is reading my CT scan?

What do I do if my GIST is Resistant?

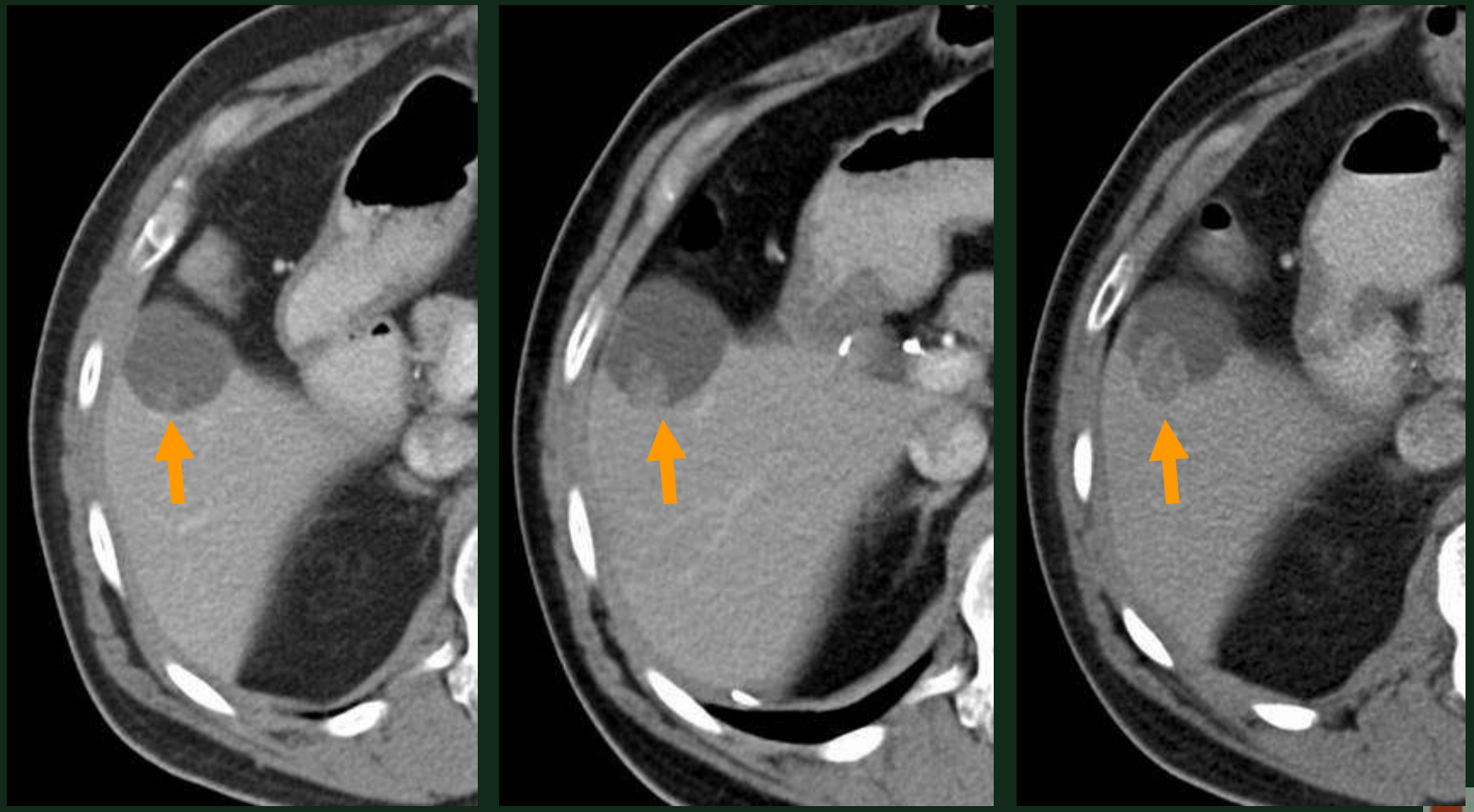
Type of Progression



Limited Progression



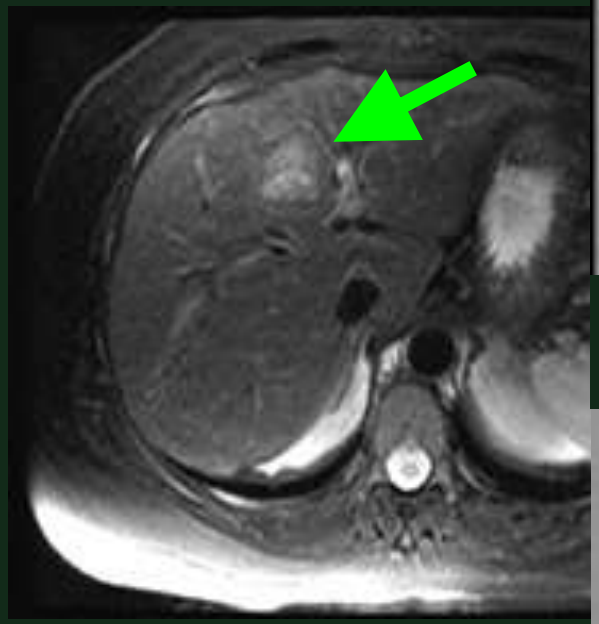
Nodular Progression

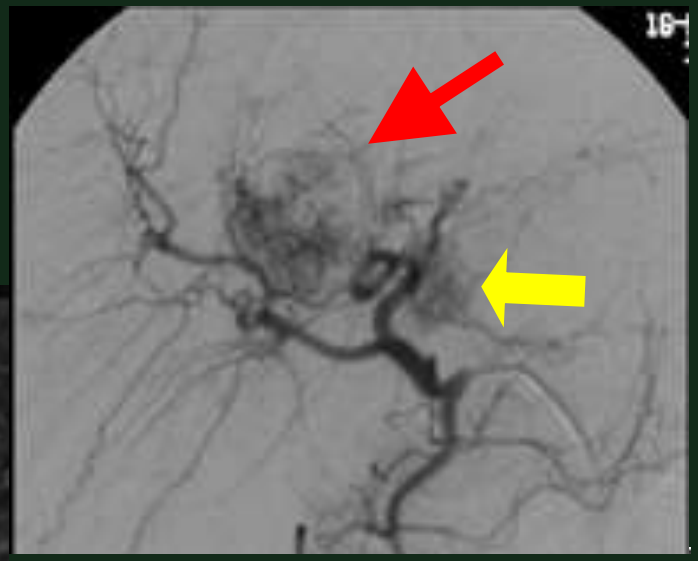


Therapy by Type of Progression

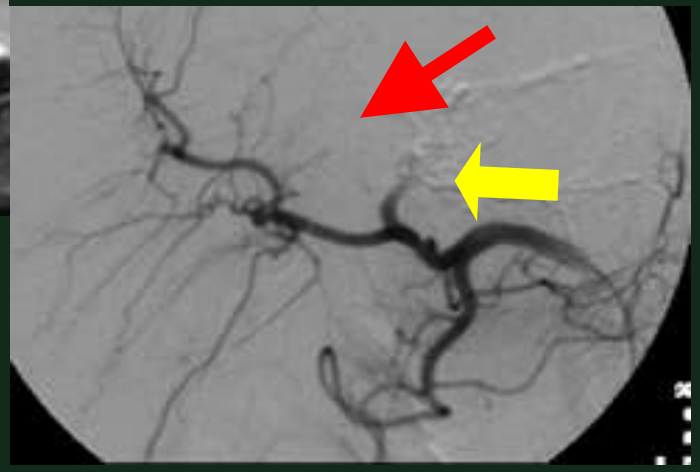
- Limited or Nodular Progression
  - Hepatic Artery Chemoembolization
  - Hepatic Radio-frequency Catheter Ablation
  - Surgical Resection
  - Radiation Therapy (esophageal or rectal)
- Widespread progression
  - Increase Imatinib to 800 mg daily
  - Sunitinib
  - Clinical Trial

Hepatic Artery Embolization





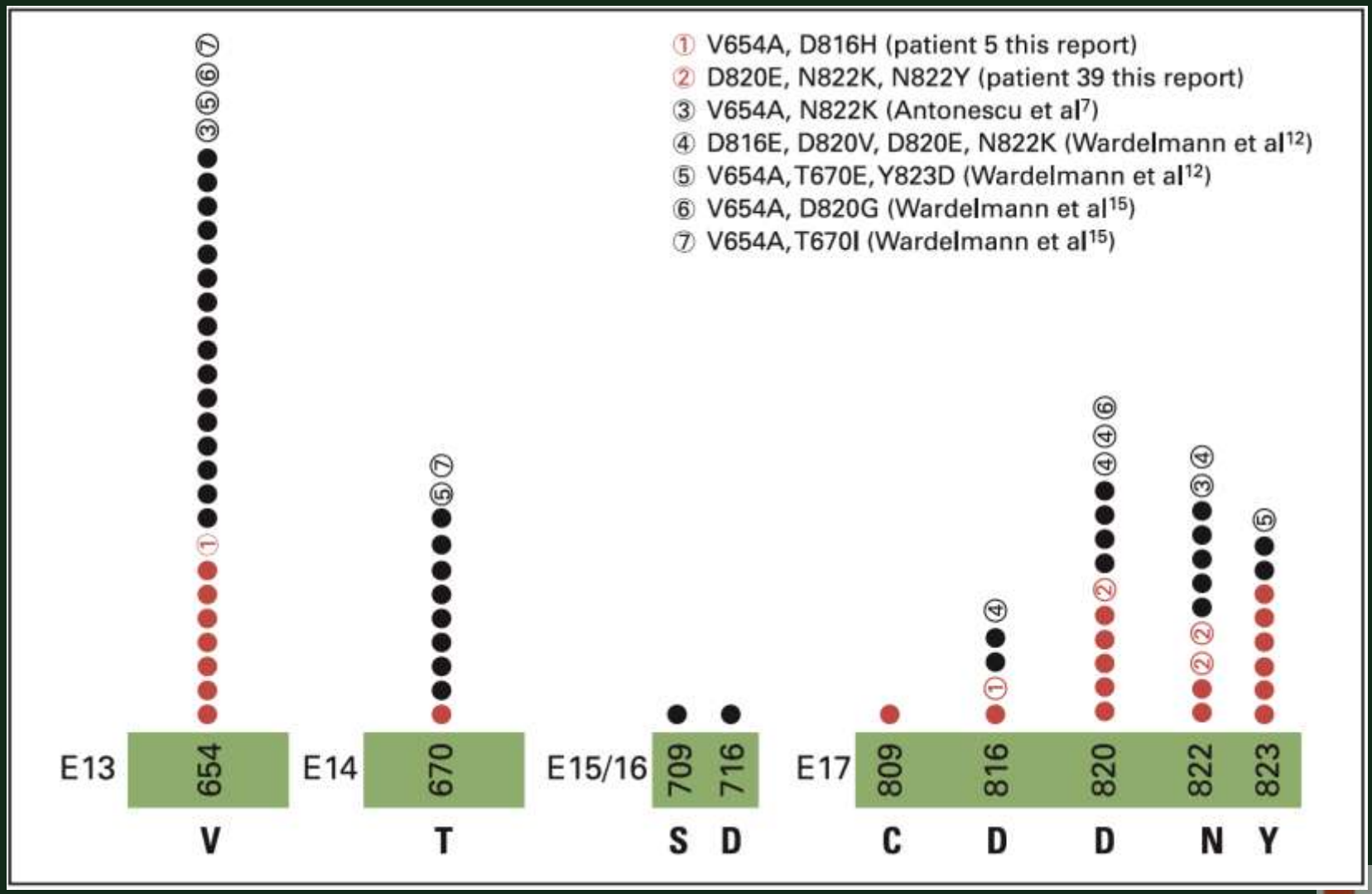
Pre-embolization



Post-embolization

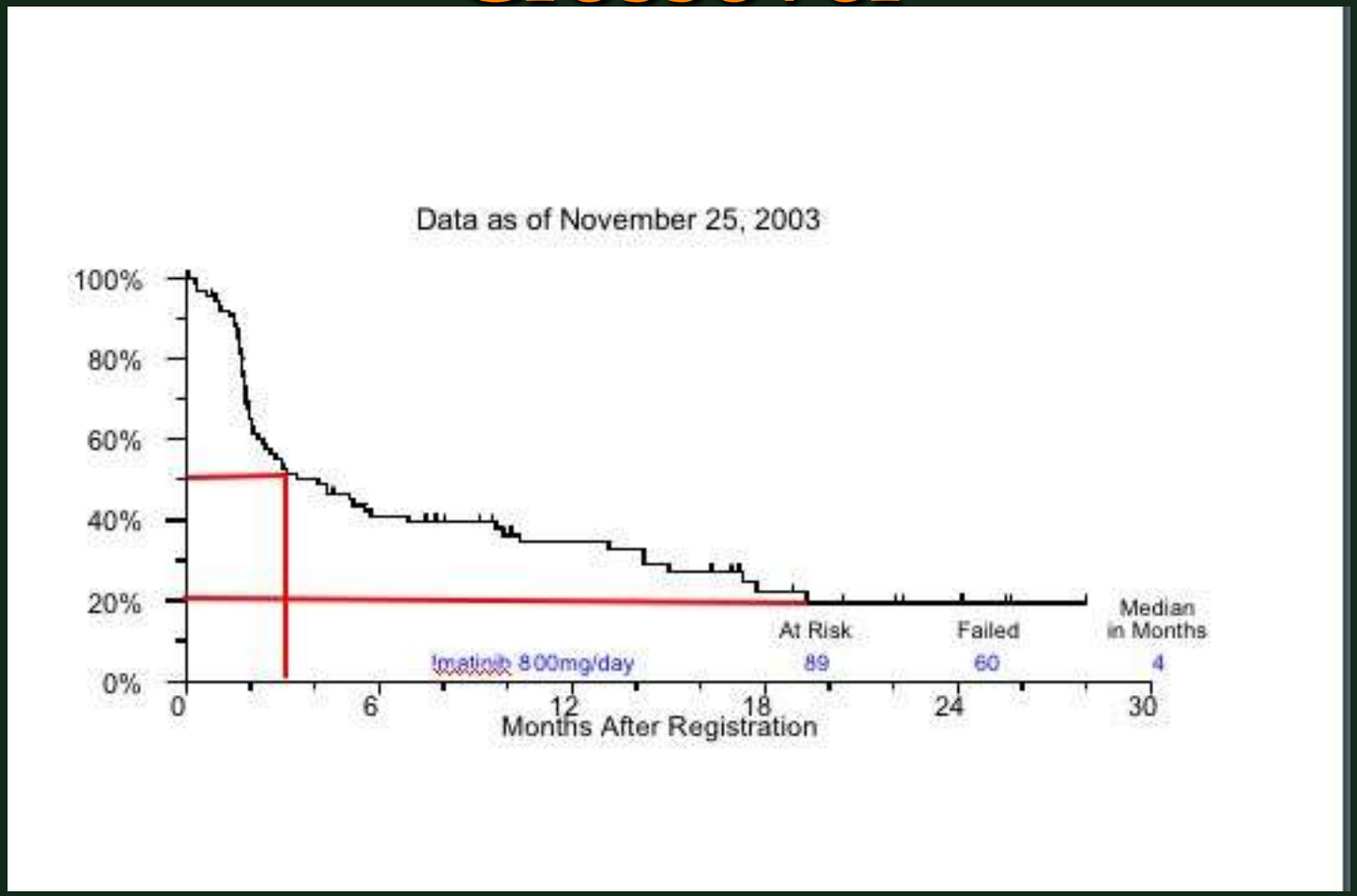
Courtesy of Dr. R. DeMatteo.

Secondary Mutation

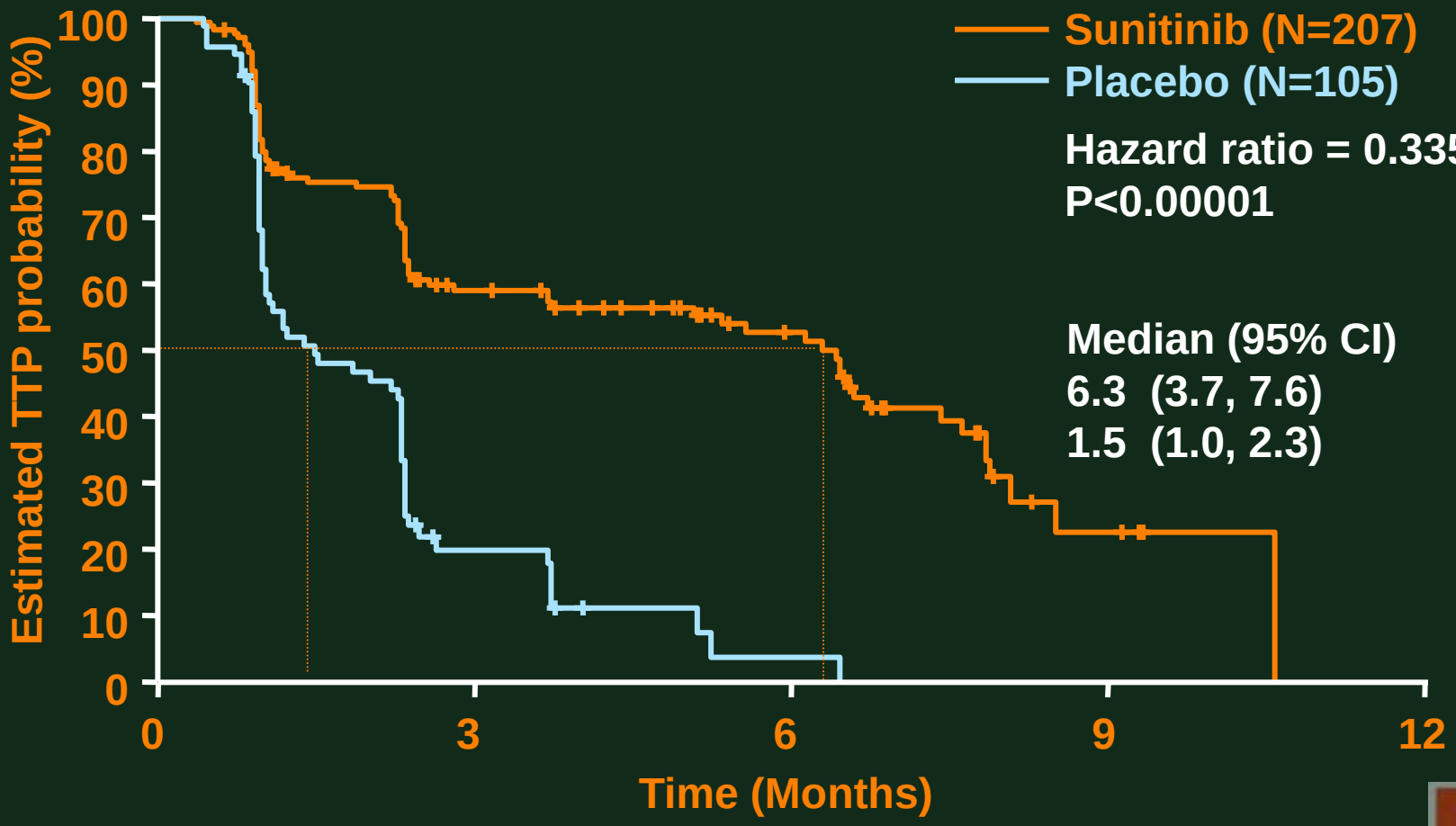


Heinrich et al, JCO 2006

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

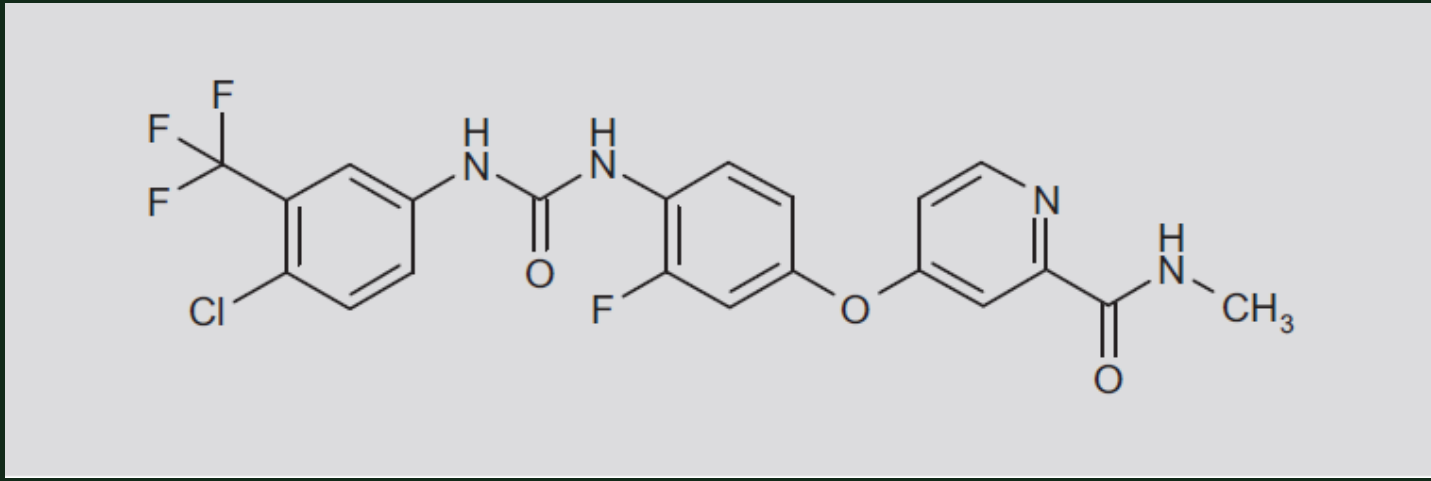


Time to Tumor Progression



Background - Regorafenib

- Regorafenib (BAY 73-4506) is a structurally distinct oral TKI with inhibitory activity against several kinases including KIT, PDGFRA, FGFR, VEGFR 2,3, TIE-2, and B-RAF.
- Regorafenib is physiologically processed into at least two bioactive metabolites, each with long half-lives (approximately 24 hrs), allowing target kinase inhibition with promising pharmacodynamics



George et al ASCO 2103

Class	Agent	Trial Phase	Results
KIT Inhibitors	Sorafenib	II	PR=13%, SD=58% PFS=5 mos.
	Dasatinib	II	PR=22%, SD=24% PFS= 2 months
	Nilotinib	I/II/III	PR=10%, SD=37% PFS=3 mos.
	Pazopanib	II	Ongoing
	Axitinib	ND	ND
	Ponatinib	ND	ND
Raf Inhib.	Vemurafenib	NA	ND
IGF-1R inh.	Linsitinib	II	Ongoing (Pedi/WT)
mTOR inh.	Everolimus	II	PR=2%, SD=43% PFS=3.5 mos.
HDAC inh.	vorinostat	NA	ND
Placebo	Various	III	PR=0% PFS=1- 1.5 months

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Should I take imatinib after my GIST was removed?

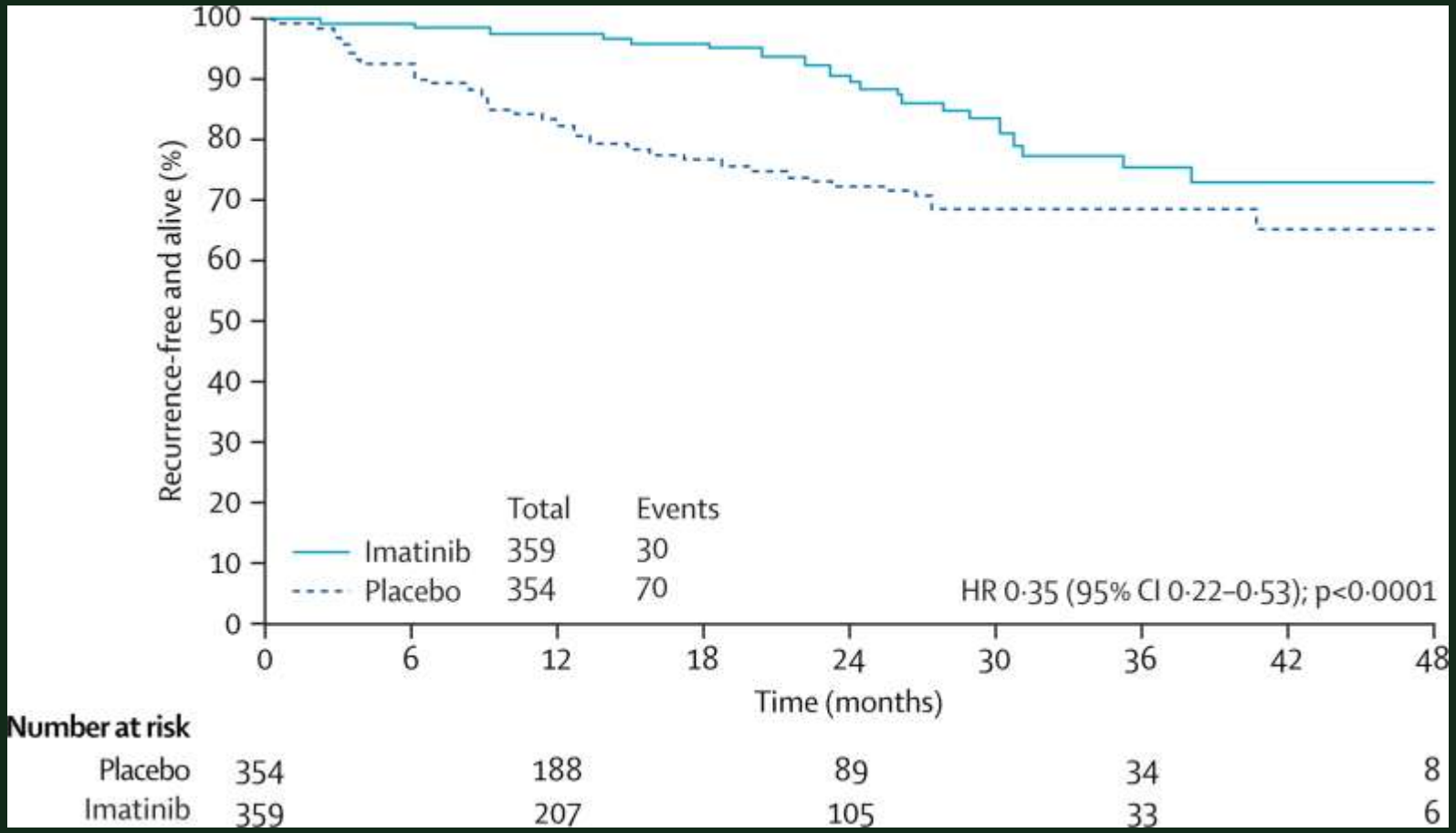
Risk Stratification of Primary GIST by Mitotic Index, Size, and Site

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.

Adjuvant Imatinib



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

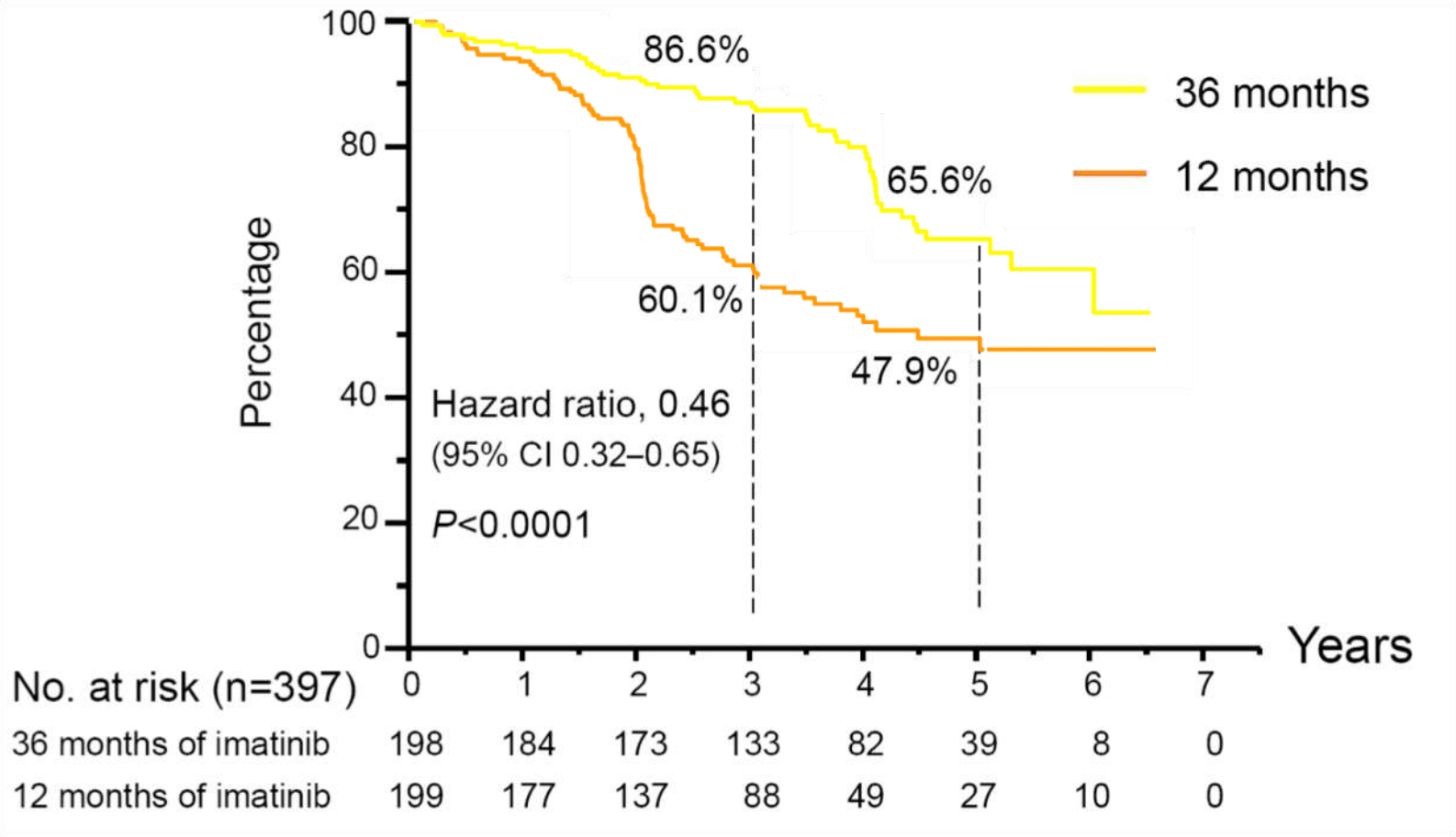
Postoperative Imatinib Studies

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.

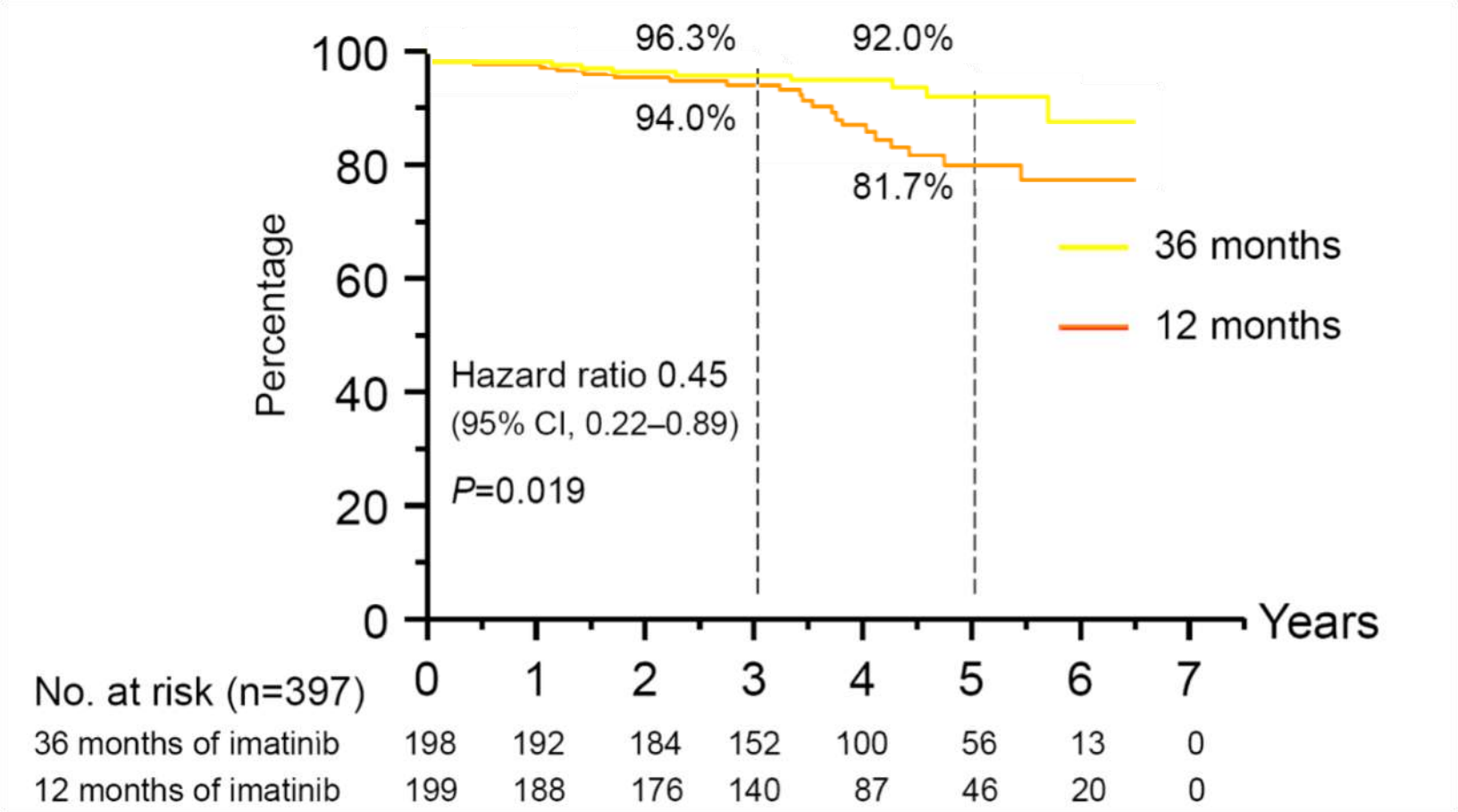
Recurrence Free Survival: 3 Years Better Than 1

Recurrence-Free Survival (ITT)
(Joensuu et al. Plenary Session: Abstract #LBA1)



Overall Survival Benefit

Overall Survival (ITT)
(Joensuu et al. Plenary Session: Abstract #LBA1)



Referral of Patients With GIST to Specialists

- Radiologists
  - Perform imaging studies: CT, MRI, and PET
- Surgeon: Biopsy and Surgical Evaluation
- Gastroenterologist: Biopsy
- Pathologist: Diagnosis and Mutation Testing
- Medical Oncologist: PCP, Systemic Therapy
- Nurse and Mid-Level: evaluate side-effects

Demetri. *J Natl Compr Canc Netw.* 2010;8:S1; Sepe. *Gastrointest Endosc.* 2009;70:254.

GIST Evaluation

- Every 2-3 months (extend over time)
- History and Physical Examination
- Laboratory Testing
- Abdominal/pelvic CT with contrast
  - Recommended for diagnosis and staging
  - Also useful for assessing common sites of metastasis (eg, liver, peritoneum)
  - Every 2-4 months while on therapy
- Chest X-ray
- ^{18}FDG-PET
- MRI with gadolinium

^{18}FDG-PET=fluorine-18-fluorodeoxyglucose positron emission tomography.

McAulliffe et al, *Annals of Surg Onc* 2009;16(4):910-9; Van den Abbeele. *Oncologist*. 2008;13:8.

Gastrointestinal Stromal Tumor (GIST)

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